2006

PEPTIDOMIMICRY: DESIGN, SYNTHESIS AND CONFORMATIONAL STUDY OF C2-SYMMETRIC OLIGOUREAS

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ABSTRACT OF DISSERTATION

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The Graduate School
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2006

PEPTIDOMIMICRY: DESIGN, SYNTHESIS AND CONFORMATIONAL STUDY OF C_2-SYMMETRIC OLIGOUREAS

ABSTRACT OF DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy
in the College of Arts and Sciences
at the University of Kentucky

By
Sihui Long

Lexington, Kentucky

Director: Dr. Arthur Cammers, Associate Professor of Chemistry

Lexington, Kentucky

2006

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Mimicking the structure and even the function of an α-peptide with artificial chain molecules such as β-peptides, γ-peptides and other unnatural oligomers has shown early success. The structural similarities between natural peptides and oligoureas lead to the belief that C_2-symmetric oligoureas could be a good candidate for peptidomimicry. Molecular modeling indicates that both homochiral (all monomers have the same absolute configuration) and alternate chiral (absolute configuration of the residues alternate) C_2-symmetric oligoureas can form helix- and sheet-like structures in solution conditionally.

Several C_2-symmetric 1,2-diamines were chosen as the building blocks for the synthesis of chiral oligoureas, and all diamines except for one were prepared in lab. Homochiral and heterochiral oligoureas based on the same diamine or mixed diamines were synthesized in the solution phase, growing a chain by adding one unit at a time to one terminus or two units at a time to both termini with 4-nitrophenoxycarbonyl (PNP)- activated and t-butoxycarbonyl (Boc) - protected diamines as the intermediates. All the chiral oligoureas were purified by either recrystallization and /or column chromatography and/ or HPLC and characterized by NMR and MALDI-MS. For some oligoureas, crystal structures were obtained. Fragment condensation was attempted to improve the efficiency of the synthesis, but this approach led to cyclized oligoureas instead of the desired concatenated residues.

Conformational studies of chiral oligoureas were done in both the solid state and the solution state. The crystal structures of some homochiral oligoureas and some alternate chiral oligoureas indicate that both helix-like structures and extended structures exist for these C_2-symmetric oligoureas. NMR and Circular Dichroism (CD) were used to study the conformation of oligoureas in solution, but the conformational study by NMR was not conclusive. CD study showed that these oligoureas have multiple conformations in solution and that some of the conformations are sensitive to solvents and temperature. Also, short homochiral and alternate chiral oligoureas based on *trans*-1,2-diaminocyclohexane (DACH) exhibit signs of cooperative behavior in solution as gauged by a series of experiments.

KEYWORDS: Peptidomimicry, Oligoureas, Circular Dichroism, Conformation, Cooperativity.

Sihui Long

June, 2006

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By

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Dedicated to

My parents, my parents-in-law and my wife

Acknowledgments

During the process of the preparation of my dissertation, I have had a lot of help from many people, directly or indirectly. I would like to take this opportunity to thank them, respectively.

Absolutely I have to thank my mentor, Dr. Arthur Cammers. It is he who took me under his wing and helped me complete the transition from a foreign student who could barely understand and speak English to a chemist who pursues the truth of chemistry with passion; and it is he who provided most of the inspiration and guidance throughout my research.

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TABLE OF CONTENTS

List of tables

List of figures

List of files

Sihui.Long.PhD.thesis.pdf	Adobe Acrobat portable document file

Chapter 1 *De Novo* Design of Peptidomimetic Oligoureas

1.1 Overview

With the remarkable chemical capabilities of biomolecules being realized, increased attention has been turned to mimicking the structure and function of natural macromolecules. Mimicking peptides (peptidomimicry) with artificial oligomers has been one of the main topics of foldamer research which is the symbolism of the trend from small molecules to medium and macromolecules. In this thesis, the author will try to convince the reader that deliberately designed C_2-symmetric chiral oligoureas can mimic the sophisticated secondary structures of natural peptides. The document is divided into 4 chapters. The first chapter explains the inspiration for this research and the logic of choosing C_2-symmetric oligoureas as a peptidomimicry candidate; Chapter 2 covers the conformational searches for target oligoureas with molecular modeling; Chapter 3 deals with the conformational study of the target oligoureas and the tool kit used to accomplish the study; Chapter 4 discusses the synthesis and characterization of the target oligoureas and other experiments.

1.2 Peptidomimicry and peptidomimetics

DNA codes for amino acids, and nature makes chains of amino acids to perform an amazing variety of tasks at the molecular level. These chains are called proteins, and their tasks include catalysis necessary for life functions, molecular recognition and structural integrity.

Another important task necessary for life is defense. It has been known for a long time that a lot of living organisms use endogenous polypeptides as host-defense against bacterial attack, and many cationic peptides have been studied in detail, for example, defensins, magainins, cecropins.[1] These antibiotic peptides are found to have two major characteristics in common.[2, 3] First, almost all of them are positively charged at neutral pH, and second, they form specific secondary structures in solution so they have a hydrophilic side as well as a hydrophobic side. For instance, Magainin, a 23-residue antibiotic peptide secreted by the skin of an African clawed frog *(Xenopus laevis),* has a net charge of +4 at neutral pH and is found to form an α-helical conformation in solution with basic and hydrophobic side chains disposed on different sides of the helix. Magainin is believed to work against pathogenic bacteria by disruption of the cellular membranes.[4] The discovery of these cationic antibiotics has given scientists hope that the long standing problem of resistance to the classic antibiotics may be solved.

Unfortunately, peptide drugs such as these are rarely successful because they tend to degrade *in vivo* via proteases and they usually have high hemolytic activity. To overcome these shortcomings, artificial oligomers which can not only mimic the structure and functions of antibiotic peptides, but also be stable to proteases, need to be created. Peptidomimicry comes into play to fulfill this mission.

Peptidomimicry is the creation of molecules which are not natural peptides but behave like them, and mimicking the secondary structures of peptide through substances with purposefully arranged functional groups. The product of peptidomimicry is called a peptidomimetic. These molecules have features similar to peptides, for example amphiphilicity, and they could be substitutes of peptide substrates of enzymes or carry out other functions of peptides.[5]

To create peptidomimetics, a series of strategies have been applied. The most common ones are modification of the side chains of amino acids and systematic replacement of backbones.[5] Other ones such as creation of scaffolds to manipulate the position of side chains, development of templates for short chain molecules to induce or stabilize secondary structures,[7,8] and introduction of constraints to control parts of the chain molecule[6] are utilized too.

Using the strategies mentioned above, numerous peptidomimetic oligomers are synthesized. These oligomers can be grouped into the following categories: α-peptides and their analogues,[9-15] β-peptides and analogues,[16-30] and γ-peptides and δ-peptides and their analogues.[31-44] (**Figure 1.1**) Among them, β-peptides show the greatest potential as peptidomimetics so far.

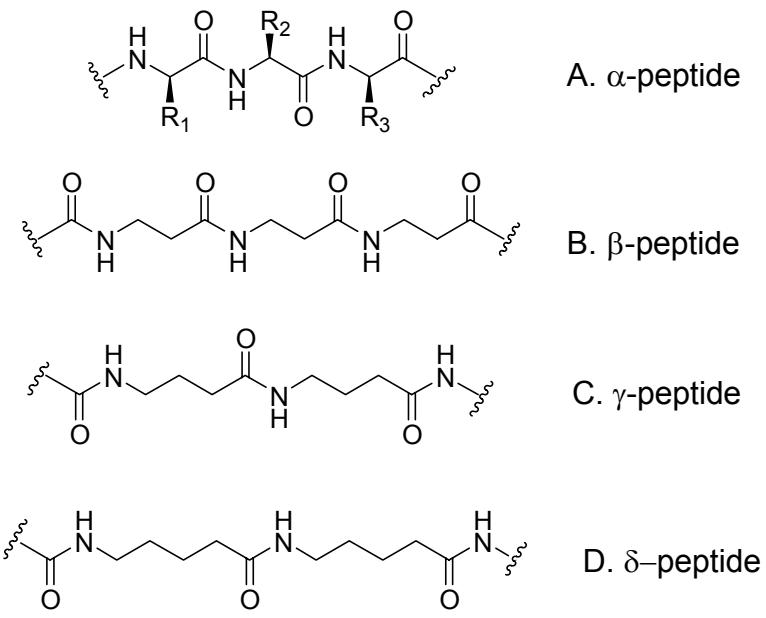
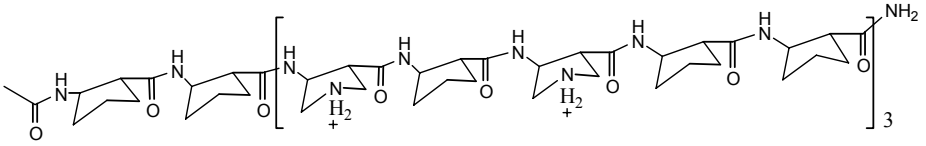
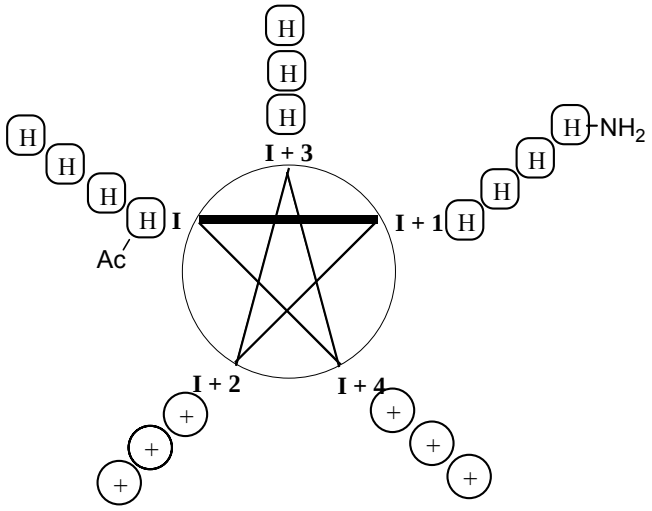


Figure 1.1 General structures of α-, β-, γ-, and δ-peptides

Inspired by the many preceding years of research in peptidomimicry, investigators envision a β-peptide world in which the molecular diversity native to natural α-peptides is reflected in β-peptides.[45] Gellman and Seebach are two of the pioneers in the research in β-peptide oligomers. They have been focusing on using β-peptides to mimic the α-peptide secondary structures and even functions of some antibiotic *α*-peptides.[46-48] They have successfully reproduced the secondary structures such as *α*-helix, β-sheet, β-turn, of natural peptides with their deliberately designed β-peptides.[49-57] One of Gellman's cationic peptides, β-17 (**Figure 1.2**), showed excellent activity against pathogenic and non-pathogenic bacteria such as *E. Faecium*, *S. aureus*, *E. Coli*, and *B. Subtilis*. The antibiotic activity appears to derive from the fact that the β-peptides fold into helices which dispose hydrophobic side chains on one side and cationic side chains on the other, similar to the magainin family of antibiotic peptides.[58,59] Based on the success of β-17, Gellman further probed the guiding principles of bioactive β-peptides. The research shows that both formation of amphiphilic helix and the ratio of cationic to hydrophobic residues are important for a β-peptide to be bioactive.[60,61]



A. Structure of β-17



B. Helical wheel diagram of β-17

Figure 1.2 Structure (A) and conformation (B) of β-17-An example of peptidomimetics

1.3 Foldamers

To emphasize the secondary structures both natural peptides and artificial oligomers form in solution, Gellman called these molecules "foldamers". According to Gellman, any polymer (natural or artificial) "with a strong tendency to adopt a specific, compact conformation" can be regarded as a foldamer.[62] This definition was modified by Moore as "any oligomer (instead of polymer) that folds into a conformationally ordered state in solution, the structures of which are stabilized by a collection of noncovalent interactions (such as Hydrogen bonding, dipole interaction, hydrophilic and hydrophobic interaction, London dispersion, and intrinsic backbone conformational preferences, etc) between nonadjacent monomer units".[5]

Natural foldamers play an important role in life processes because biomacromolecules (proteins, nucleic acids, polysaccharides) rely on stable, complex 3D architecture based on foldmeric units (α-helices, β-sheets, β-turns, β-barrels, and ω-loops) to carry out most of their functions.[63] Chasing nature is one of the instincts of human beings. Ever since the fascinating chemistry of biopolymers was appreciated, chemists have set out to create synthetic foldamers by *de novo* design. With the scientific and technological foundation of foldamer study laid in the early 20th century during the rise of modern synthetic polymer chemistry,[64] molecular biology

and supramolecular chemistry,[65,5] as well as developments in NMR, CD, crystallography and molecular modeling, plus the factors that control the conformations of biofoldamers coming to light,[62] major breakthroughs came along over the past two decades.

In addition to peptidomimetic foldamers, nucleotidomimetic foldamers,[66-68] (**Figure 1.3**) single-stranded and multi-stranded abiotic foldamers [69-77] also have been synthesized.

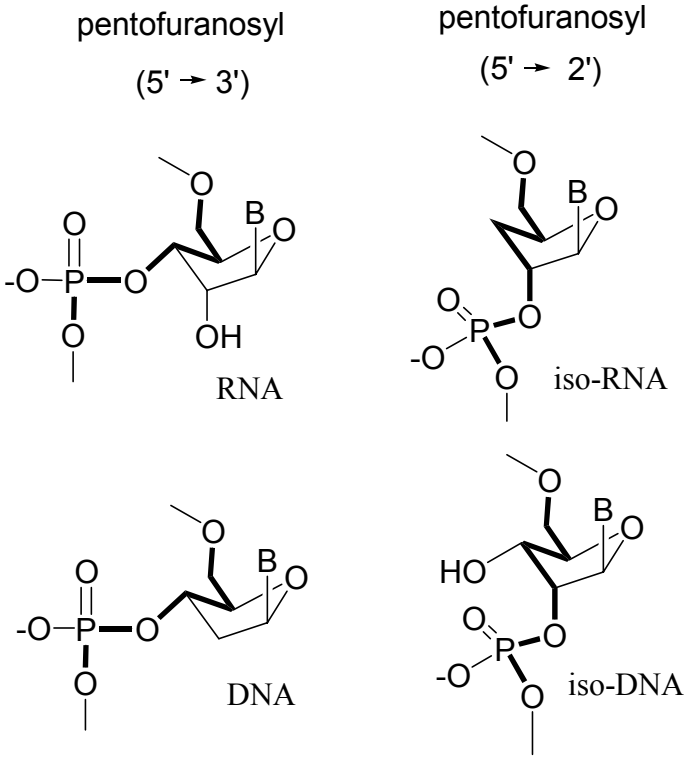


Figure 1.3 Nucleotidomimetics: An example of backbone modification

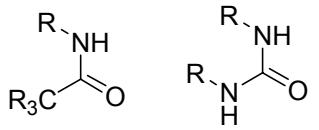
1.4 Oligoureas as peptidomimetic foldamers

The success of peptidomimetic foldamers based on unnatural backbones suggests oligoureas could be a good peptidomimetic foldamer candidate. This aim is the subject of this thesis. We wish to explore the conformational propensities of C_2 symmetric oligoureas of chiral C_2 symmetric diamines. Such a study could be a starting point for an "oligourea world".

1.4.1 Oligoureas versus peptides: comparison

What makes peptides peculiar is their ability to form specific conformations in solution, and this conformational stability depends on the length of the chains. A major question to ask is whether or not chiral oligoureas behave like foldamers. Another major question is whether oligoureas can be designed to perform useful mimicry of peptides.

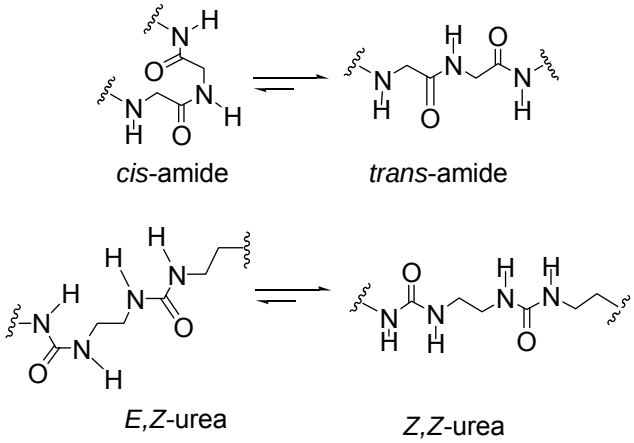
Between the general structures of an amide and a urea, the similarities are obvious. Both N-C=O and aliphatic components are present, and a urea can act as a hydrogen bond donor (NH) as well as a hydrogen bond acceptor(C=O), just as an amide does (**Figure 1.4**).



Amide **Urea**

Figure 1.4 Structural similarity between amide and urea

In peptides, generally the *trans*-amide is preferred over the *cis*-conformer. The global conformation is controlled by the preference for *trans*-amides, except for proline residues which have a certain conformational ambiguity. For example, in acyclic peptide residues, the *trans*-amide conformer is about 2.8 kcal/mol lower in energy than the corresponding *cis*-amide.[78] Similarly, oligoureas tend to adopt the Z,Z-conformer instead of the E,Z-conformer because of the energy difference. Accordingly, the global conformation of oligoureas should be edited by this preference (**Figure 1.5**).



cis-amide *trans*-amide

E,Z-urea *Z,Z*-urea

Figure 1.5 Conformational control by backbone NCO in amide and urea

Although side chain control of peptide conformation is context-dependent and never absolute, sidechain-sidechain interactions play another important role in the "folding" of peptides.[79-81] For example, Ala tends to stabilize helical conformation in peptides, and Lys at the C terminus also has a helix-stabilizing effect.

In the design of conformation in oligoureas, side chains can be utilized to manipulate the conformation by carefully selecting monomeric diamines. A series of diamines (**1**-**5**) (**Figure**

1.6) have been chosen as the building blocks for the target oligoureas. Each has a specific conformational consideration. For example, the diphenyl substituents in **2** should favor the double gauche instead of the triple gauche conformations shown in **Figure 1.7**. However, the chain can be liberated by inclusion of achiral, unsubstituted **5** which would play a similar role as the Gly residues in α-peptide chains. The other monomeric units proposed are cyclic and should provide an analogous level of control to that of proline residues in α-peptide chains. This effect should not be excessive because the conformational argument of polyproline is complex and ubiquitous in living systems.[82-84]

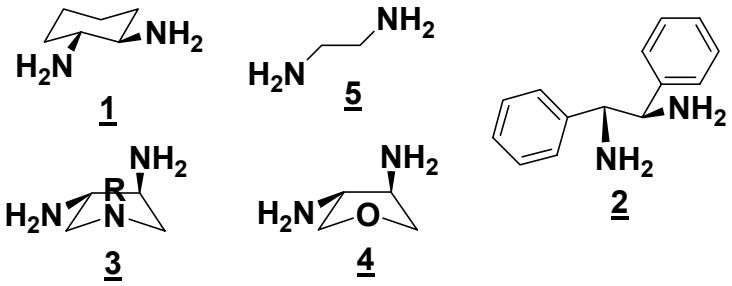


Figure 1.6 Chosen C_2-symmetric diamines

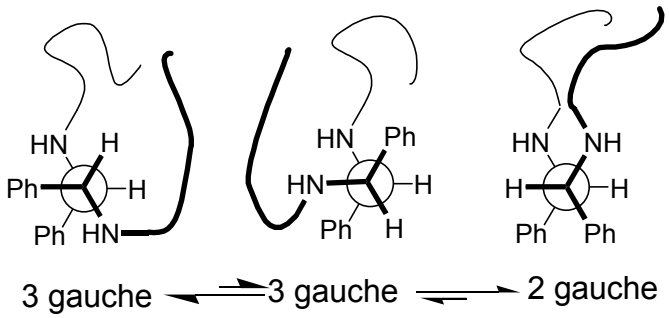


Figure 1.7 Gauche interaction should lead to conformational preference

Besides the likeness between the target oligoureas and peptides, they do have their differences. In the peptide backbone, the amide bond (ω bond) exerts much conformational control *via* amidic resonance. However, the rotational barriers of the analogous C-N bonds of ureas have much decreased barriers to rotation such that they tend to be dynamic on the NMR time scale at room temperature. For example, the barriers of *N,N*-dimethylurea about the Me_2N-CO and H_2N-CO are 11.0 and 10.6 kcal/mol respectively.[85] This contrasts sharply with the corresponding rotational barrier of *N,N*-dimethylformamide, 21 kcal/mol.[86] On the other hand, oligoureas, arrayed to form hydrogen bonding interactions, have similar rotation barriers,

but strongly maintain inter-chain associations.[87] Urea chains probably have an increased tendency to engage in intramolecular hydrogen bonding, but this has not been rigorously evaluated because this comparison would likely be of the apple-versus-orange variety.

Unlike α-peptides and β-peptides, the interaction between the carbonyl moieties in the oligoureas is rather enforced, so two urea carbonyls linked to amines on the same monomer will prefer to point in opposite directions to minimize the local dipole moment. A solvent effect for the conformation might be expected. For example, might water be expected to allow parallel alignment of the urea carbonyls? Furthermore, does the combination of the gauche preference, carbonyl dipole interactions, hydrogen bonding and the ZZ urea effect result in one global conformation or a limited set of global conformations that would allow a platform for the design of interesting oligomers? Does the C_2 local chirality of the monomer give rise to global C_2 chirality (helical)?

Additive field effects of aligned amide carbonyls of α-peptides in the α-helix conformation give rise to a macrodipole moment which exerts control on the conformation and affects interactions with sidechains, protein domains, and solvent.[88-93] The destabilizing effect of the macrodipole is offset by hydrogen bonding and solvation. The additive dipole moment of carbonyl groups likely controls conformation in α- and β-peptides less than it would control conformation in the oligomers proposed. Even though the primary structure of α-peptides separates carbonyl groups by two atoms, and in β-peptides by three atoms, these oligomers allow the chain to spiral loosely whereas the turns in the proposed oligomers are predicted to be tighter. For example the α-helix has a 3.6-residue period whereas the period of the oligomers under study is predicted to be ~ 3.0 residues.

1.4.2 Oligourea study: history and status quo

Although homopolymers of ureas had long been known, the search for secondary structures by systematic studies on specific oligoureas didn't begin until 1992, when Nowick and co-workers investigated the conformations of acyclic *N,N*-linked oligoureas with the repeating unit [-N(CONHR)-$(CH_2)_2$-]. This molecule showed interesting conformation in solution due to intramolecular Hydrogen bonding[94-96] (see **Figure 1.8**).

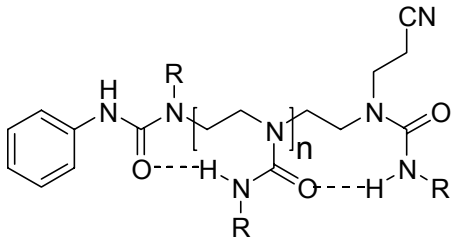


Figure 1.8 *N,N*-linked oligourea

With the search for new backbones as peptidomimetics going on in the 1990s, the interest in *N,N'*-linked oligoureas has grown. Almost simultaneously, Burgess, Nowick and Schultz attempted to synthesize these oligoureas on the solid phase.[97-99] Despite all the synthetic efforts, the question whether oligoureas should have conformation in common with peptides hadn't been answered until a series of seminal papers were published by Guichard. [100-102]

Guichard and co-workers concentrated on mimicking peptides with short chain *N,N'*-linked oligoureas bearing proteinogenic side chains (**Figure 1.9**). Through 2D NMR and CD, they have shown that these molecules can form helical conformation in protic solution. The dominant conformation of Guichard's oligoureas was found to mimic helices adopted by γ-peptides.

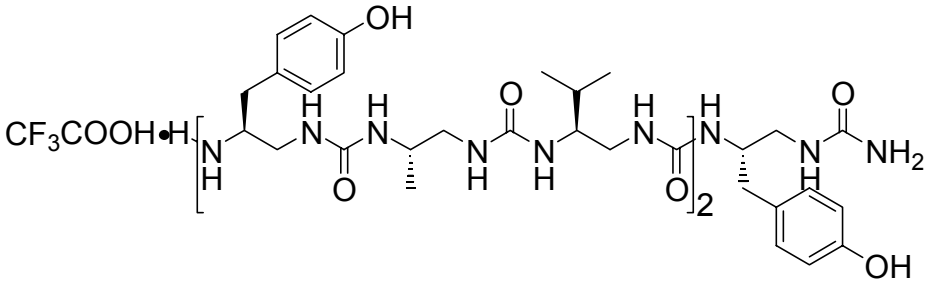


Figure 1.9 One of Guichard's biomimetic oligoureas

In addition to conformational studies of oligoureas, oligoureas could have pharmaceutical potential. As known, urea bonds have already been used as important structural elements in enzyme inhibitors and as switching points in retro-inverso peptidomimetics in medicinal chemistry.[103,104] Also, oligomers possessing segments of both bioactive peptide and chiral oligourea should result in extended *in vivo* stability, because peptidases need either specific sequences, extended structure or the peptide C terminus to catalyze cleavage. This could overcome the *in vivo* instability shortcoming of peptide antibiotics.

Among the early studies, a Tat-derived oligourea not only showed high affinity and specificity toward TAR RNA, similar to Tat peptides, but also exhibited tremendous proteolytic stability.[105]

1.4.3 C_2-symmetric oligoureas

Guichard's research on the conformation of proteinogenic side chains bearing *N,N'*-linked oligoureas shows that mimicking the secondary structures of peptides with these molecules is possible. This study focused on C_2-symmetric oligoureas to simplify the conformation of the chain in order to better define the conformational dynamics and preferred conformation. A peptide has two different ends, an N terminus and a C terminus, while a C_2-symmetric oligourea has two identical termini. This makes it simpler for oligoureas when secondary structure is formed. Take the helix formation as an example. In both a peptide and a C_2-symmetric oligourea, helices are nucleating in a bidirectional manner at the center of a peptide and at the center of an oligourea. The conformation propagating from the center of the peptide has a top and a bottom; the residues are chiral, so each residue must contribute distinctly to the stability of the helix. This is true for the simplest homologous sequence of α-amino acids—even Gly_n. However, for the oligourea, the propagation of helical conformation is two-fold symmetric.

Both Guichard's oligoureas and the proposed C_2-symmetric oligoureas have four atoms to separate the carbonyl groups, but Guichard's oligoureas are arguably more complex than the proposed C_2-symmetric oligoureas because only one α-carbon is substituted; therefore no symmetry is possessed, and directionality is expected.

Although symmetry is enforced on the target molecules by design, diversity is planned, both in structure and chirality (**Figure 1.10**).

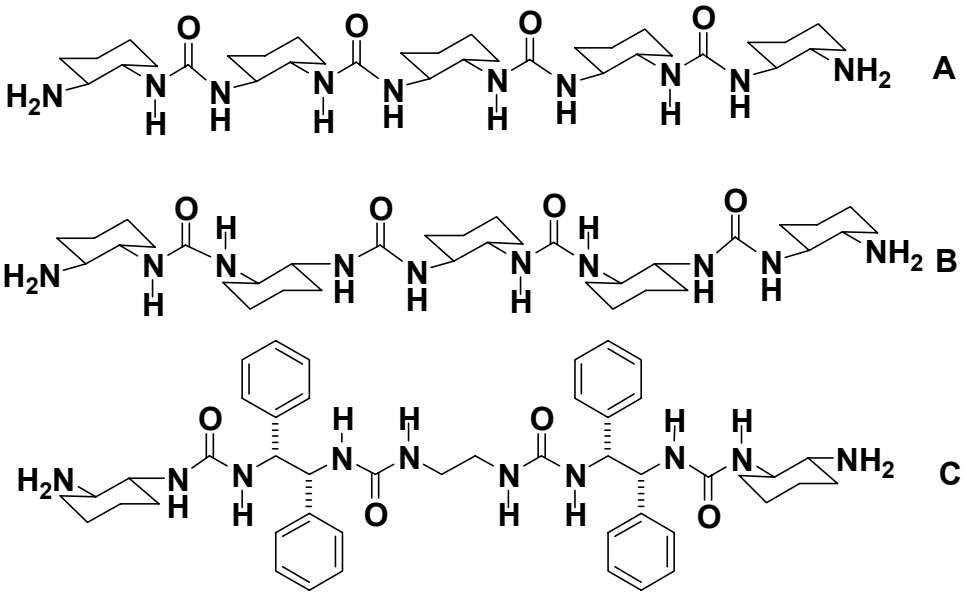


Figure 1.10 Examples of oligoureas designed
A. Homochiral, homostructural pentaurea
B. Heterochiral, homostructural pentaurea
C. Homochiral, heterostructural pentaurea

In foldamer design, sequence heterogeneity is required for a foldamer to favor one tertiary structure over another, but for the first stage foldamer investigation which mainly deals with secondary structures, homogenous oligomers can provide the necessary conformational diversity. [62]

Since the factors which control the conformation of α-peptides exist in the oligoureas as well, helical and extended conformations (**Figure 1.11**) are expected for oligoureas, but a major question to ask is whether or not local structural change will affect the overall conformational propensity of the chain. Conformational study of oligoureas consisting of both the same monomer (homostructural) and different monomers (heterostructural) should answer the question.

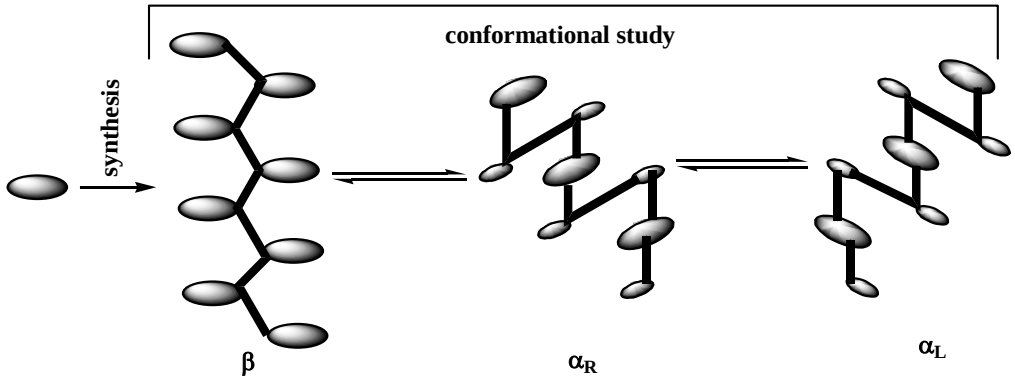


Figure 1.11 C_2-symmetric diamines lead to C_2-symmetric oligoureas, possible conformations include extended β and two helical α structures

Though natural peptides are almost exclusively composed of L-amino acids, in peptide motif design, D-amino acids are included in L-amino acid chains to influence the conformation.[106, 107] Similarly, residue chirality should exert impact on the global conformation of the oligourea chains. For example, inclusion of (S,S) monomers in (R,R) chains might change the overall conformation of the chain molecule. Chirality-conformation relationship should be figured out by investigating both homochiral (all the monomers have the same absolute configuration) and heterochiral (not all the monomers have the same absolute configuration) oligourea chains.

Cooperativity, which is an expression of the relative stability of the conformational motif as a function of chain length, is essential to the complex functions of biomolecules.[62] Questions to be answered by this work include: how large can these molecules be made and what advantages are there in elongating the chains? At what point do the returns diminish? What is the effect of chain length in the ability of these oligomers to bind molecular guests? Answering these questions will assess the cooperativity in the conformation of these oligomers.

In addition to conformational study, practical applications have been anticipated too. For example: through hydrogen bonding and other noncovalent interactions, these oligoureas could act as molecular hosts for anions; when a helix is formed, it should have a hydrophilic internal and hydrophobic external molecular surface area, so by including the oligoureas in hydrophobic membranes and on polymeric solid supports, signal transduction might be achieved (This avenue was explored by my colleague Ms. Amanda Watts. A portion of her thesis is based on material synthesized in the current work. Her thesis should be listed as 2006 or 2007. At the

time this thesis was submitted to the University of Kentucky Graduate School, Ms Watts' thesis had not yet been submitted.).

Oligourea segments might be able to modify short tracts of biologically active peptides; more importantly, synthesizing chains by combinatorially including residues **1-5** with a focus on the targets possessing the periodic appearance of the basic residue **3** (or versions with an extended basic side chain) in a helical or extended conformation may optimally mimic antibiotic peptides. Residue **3** will be extended at the pyrrolidine N atom with solubilizing sidechains and /or cationic and anionic sidechains to increase the potential diversity of the proposed oligomers.

1.5 Conclusion

β-Peptides and other artificial oligomers have been shown to be good peptidomimetic foldamer motifs so far. Can chiral oligoureas mimic α-peptides too? The structural similarities between a urea and an amide give the first impression that oligoureas could be a good peptidomimetic, and asymmetric, proteinogenic side chain bearing oligoureas have been proven to form helices in organic solvents. Another member of the oligourea family, the even simpler, C_2-symmetric chiral oligoureas should also be able to mimic the conformations of natural peptides. This hypothesis will be confirmed by computation and experiment results.

1.6 References

(1) Boman, H. G. *Ann. Rev. Immunol.* **1995**, *13*, 61.

(2) Hancock, R. E. W.; Farmer, S. W. *Antimicrob. Agents Chemother.* **1993**, *37*, 453.

(3) Hancock, R. E. W. *Lancet* **1997**, *349*, 418.

(4) Matsuzaki, K.; Sugishita, K.; Harada, M.; Fujii, N.; Miyajima, K. *Biochim. Biophys. Acta* **1997**, *1327*, 119.

(5) Hill, D.; Mio, M.; Prince, R.; Hughes, T.; Moore, J. *Chem. Rev*. **2001**, *101*, 3893.

(6) Rizo, J.; Gierasch, L. M. *Ann. Rev. Biochem.* **1992**, *61*, 387.

(7) Schneider, J. P.; Kelly, J. W. *Chem. Rev.* **1995**, *95*, 2169.

(8) Nowick, J. S.; Smith, E. M.; Pairish, M. *Chem. Soc. Rev.* **1996**, *25*, 401.

(6) Applequist, J.; Bode, K.; Appella, D.; Christianson, L.; Gellman, S. *J. Am. Chem. Soc*. **1998**, *120*, 4891.

(7) Porter, E. A.; Wang, X.; Lee, H. S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 298.

(8) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc*. **2002**, *124*, 7324.

(9) Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9367.

(10) Mohle, K.; Hofmann, H.-J. *Biopolymers* **1996**, *38*, 781.

(11) Kirshenbaum, K.; Barron, A. E.; Goldsmith, R. A.; Armand, P.; Bradley, E. K.; Truong, K. T. V.; Dill, K. A.; Cohen, F. E.; Zuckermann, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4303.

(12) Armand, P.; Kirshenbaum, K.; Falicov, A.; Dunbrack, R. L.; Dill, K. A.; Zuckermann, R. N.; Cohen, F. E. *Folding Des.* **1997**, *2*, 369.

(13) Smith, A. B., III; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672.

(14) Smith, A. B., III; Guzman, M. C.; Sprengeler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947.

(15) Lucarini, S.; Tomasini, C. *J. Org. Chem.* **2001**, *66*, 727.

(16) Graf, R.; Lohaus, G.; Borner, K.; Schmidt, E.; Bestian, H. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 481.

(17) Kovacs, J.; Ballina, R.; Rodin, R. L.; Balasubramanian, D.; Applequist, J. *J. Am. Chem. Soc.* **1965**, *87*, 119.

(18) Bestian, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 278.

(19) Schmidt, V. E. *Angew. Makromol. Chem.* **1970**, *14*, 185.

(20) Matthews, J. L.; Overhand, M.; Kuhnle, F. N. M.; Ciceri, P. E.; Seebach, D. *Liebigs Ann.* **1997**, 1371.

(21) Seebach, D.; Matthews, J. L.; Meden, A.; Wessels, T.; Baerlocher, C.; McCusker, L. B. *Helv. Chim. Acta* **1997**, *80*, 173.

(22) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913.

(23) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015.

(24) Seebach, D.; Albert, M.; Arvidsson, P. I.; Rueping, M.; Schreiber, J. V. *Chimia* **2001**, *55*, 345.

(25) Yang, D.; Ng, F.-F.; Li, Z.-J. *J. Am. Chem. Soc.* **1996**, *118*, 9794.

(26) Gennari, C.; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2067.

(27) Moree, W. J.; van der Marel, G. A.; Liskamp, R. J. *J. Org. Chem.* **1995**, *60*, 5157.

(28) Gude, M.; Piarilli, U.; Potenza, D.; Salom, B.; Gennari, C. *Tetrahedron Lett.* **1996**, *37*, 8589.

(29) Monnee, M. C. F.; Marijine, M. F.; Brouwer, A. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **2000**, *41*, 7991.

(30) Gunther, R.; Hofmann, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 247.

(31) Kajtar, M.; Bruckner, V. *Tetrahedron Lett.* **1966**, *7*, 4813.

(32) Kajtar, M.; Hollosi, M. *Acta Chim. Acad. Sci. Hung.* **1970**, *65*, 403.

(33) Rydon, H. N. *J. Chem. Soc.* **1964**, 1328.

(34) Watanabe, T.; Ina, T.; Ogawa, K.; Matsumoto, T.; Sawa, S.; Ono, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3939.

(35) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568.

(36) Moran, E. J.; Wilson, T. E.; Cho, C. Y.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P. A.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Biopolymers* **1995**, *37*, 213.

(37) Cho, C. Y.; Moran, E. J.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P. A.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science* **1993**, *261*, 1303.

(38) Cho, C. Y.; Youngquist, R. S.; Paikoff, S. J.; Beresini, M. H.; Herbert, A. R.; Berleau, L. T.; Liu, C. W.; Wemmer, D. E.; Keough, T.; Schultz, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7706.

(39) Lin, P.; Ganesan, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 511.

(40) von Roedern, E. G.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 687.

(41) von Roedern, E.G.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156.

(42) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S.; Sharma, J. A. R. P.; Ravikanth, V.; Diwan, P. V.; Nagaraj, R.; Kunwar, A. C. *J. Org. Chem.* **2000**, *65*, 6441.

(43) Szabo, L.; Smith, B. L.; McReynolds, K. D.; Parrill, A. L.; Morris, E. R.; Gervay, J. *J. Org. Chem.* **1998**, *63*, 1074.

(44) Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *Chem. Commun.* **1998**, 2041.

(45) Seebach, D.; Beck, A.; Rueping, M.; Schreiber, J. V.; Sellner, H. *Chimia* **2001,** 55, 98.

(46) Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1223.

(47) Werder, M.; Hauser, H.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1774.

(48) Porter, E. A.; Wang, X.; Lee, H.-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.

(49) Muller, H.-M.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 477.

(50) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071.

(51) Krauthauser, S.; Christianson, L. A.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1997**, *119*, 11719.

(52) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1595.

(53) Chung, Y. J.; Christianson, L. A.; Stanger, H. E.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 10555.

(54) Chung, Y. J.; Huck, B. R.; Christianson, L. A.; Stanger, H. E.; Krauthauser, S.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 3995.

(55) Huck, B. R.; Fisk, J. D.; Gellman, S. H. *Org. Lett.* **2000**, *2*, 2607.

(56) Hanessian, S.; Yang, H. *Tetrahedron Lett.* **1997**, *38*, 3155.

(57) Motorina, I. A.; Huel, C.; Quiniou, E.; Mispelter, J.; Adjadj, E.; Grierson, D. S. *J. Am. Chem. Soc.* **2001**, *123*, 8.

(58) Porter, E. A.; Wang, X.; Lee, H-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, 565.

(59) Matsuzaki, K.; Sugishita, K.-I.; Fujii, N. *Biochemistry* **1995,** *34*, 3423.

(60) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 7324.

(61) Raguse, T. L.; Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 12774.

(62) Gellman, S. H. *Acc. Chem. Res*. **1998**, *31*, 173.

(63) Sanford, A. R.; Yamato, K.; Yang, X.; Yuan, L.; Han, Y.; Gong, B. *Eur. J. Biochem.* **2004,** *271*, 1416.

(64) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, NY, 1953.

(65) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinhem, Germany, 1995.

(66) Dougherty, J. P.; Rizzo, C. J.; Breslow, R. *J. Am. Chem. Soc.* **1992**, *114*, 6254.

(67) Hashimoto, H.; Switzer, C. *J. Am. Chem. Soc.* **1992**, *114*, 6255.

(68) Kierzek, R.; He, L.; Turner, D. H. *Nucleic Acids Res.* **1992**, *20*, 1685.

(69) Bassani, D. M.; Lehn, J.-M. *Bull. Chem. Soc. Fr.* **1997**, *134*, 897.

(70) Bassani, D. M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1845.

(71) Ohkita, M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem. Eur. J.* **1999**, *5*, 3471.

(72) Ohkita, M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Heterocycles* **2000**, *52*, 103.

(73) Kagechika, H.; Azumaya, I.; Tanatani, A.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1999**, *40*, 3423.

(74) Lokey, R. S.; Iverson, B. L. *Nature* **1995**, *375*, 303.

(75) Archer, E. A.; Gong, H.; Krische, M. J. *Tetrahedron* **2001**, *57*, 1139.

(76) Nowick, J. S.; Chung, D. M.; Maitra, K.; Maitra, S.; Stigers, K. D.; Sun, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7654.

(77) Nowick, J. S.; Tsai, J. H.; Bui, Q.-C. D.; Maitra, S. *J. Am. Chem. Soc.* **1999**, *121*, 8409.

(78) Deetz, M. J.; Fahey, J. E.; Smith, B. D. *J. Phys. Org. Chem.* **2001,** *14*, 463.

(79) Creamer, T. P.; Rose, G. D. *Proc. Natl. Acad. Sci.* **1992,** *89*, 5937.

(80) Finer Moore, J. S.; Fauman, E. B.; Stroud, R. M. *Protein Eng.* **1996,** *9*, 69.

(81) Gallivan, J. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **2000,** *122*, 870.

(82) Jenkins, C. L.; Lin, G.; Duo, J.; Rapolu, D.; Guzei, I. A.; Raines, R. T.; Krow, G. R. *J. Org. Chem.* **2004,** *69*, 8565.

(83) Kelly, M. A.; Chellgren, B. W.; Rucker, A. L.; Troutman, J. M.; Fried, M. G.; Miller, A.-F.; Creamer, T. P. *Biochemistry* **2001,** *40*, 14376.

(84) Chellgren, B. W.; Creamer, T. P. *J. Am. Chem. Soc.* **2004,** *126*, 14734.

(85) Haushalter, K. A.; Lau, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1996,** *118*, 8891.

(86) Rabinovitz, M.; Pines, A. *J. Am. Chem. Soc.* **1969**, *91*, 1585.

(87) Vysotsky, M. O.; Pop, A.; Broda, F.; Thondorf, I.; Böhmer, V. *Chem. Eur. J.* **2001,** *7*, 4403.

(88) Motoshima, H.; Mine, S.; Masumoto, K.; Abe, Y.; Iwashita, H.; Hasimoto, Y.; Chijiiwa, Y.; Ueda, T.; Imoto, T. *J. Biochem.* **1997,** *121*, 1076.

(89) Joshi, H. V.; Meier, M. S. *J. Am. Chem. Soc.* **1996,** *118*, 12038.

(90) Munoz, V.; Serrano, L. *J. Mol. Biol.* **1995,** *245*, 275.

(91) Niwa, M.; Murata, T.; Kitamastu, M.; Matsumoto, T.; Higashi, N. *J. Mater. Chem.* **1999,** *9*, 343.

(92) Higashi, N.; Nishikawa, R.; Koga, T.; Niwa, M. *J. Colloid and Interface Sci.* **1999,** *220*, 362.

(93) Hart, S. A.; Bahadoor, A. B. F.; Matthews, E. E.; Qiu, X. Y. J.; Schepartz, A. *J. Am. Chem. Soc.* **2003,** *125*, 4022.

(94) Nowick, J. S.; Powell, N. A.; Martinez, E. J.; Smith, E. Em.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 3763.

(95) Nowick, J. S.; Abdi, M.; Bellamo, K. A.; Love, J. A.; Martinez, E. J.; Noronha, G.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 89.

(96) Nowick, J. S.; Mahrus, S.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 1066.

(97) Burgess, K.; Linthicum, D. S.; Shin, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 907.

(98) Wilson, M. E.; Nowick, J. S. *Tetrahedron Lett.* **1998**, *39*, 6613.

(99) Kim. J.; Bi, Y.; Paikoff, S. J.; Schultz, P. G. *Tetrahedron Lett.* **1996**, *37*, 5305.

(100) Semetey, V.; Rognan, D.; Hemmerlin, C.; Graff, R.; Briand, J-P.; Marraud, M.; Guichard, G. *Angew. Chem., Int. Ed*. *Engl.* **2002**, *41*, 1893.

(101) Hemmerlin, C.; Marraud, M.; Rognan, D.; Semetey, V.; Briand, J-P.; Guichard, G. *Helv. Chim. Acta* **2002**, *85*, 3692.

(102) Violette, A.; Averland-Petit, M. C.; Semetey, V.; Hemmerlin, C.; Casimir, R.; Graff, R.; Marraud, M.; Briand, J-P.; Rognan, D.; Guichard, G. *J. Am. Chem. Soc.* **2005**, *127*, 2156.

(103) Lam, P. Y. S.; Jadhaw, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C. H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson, -Viitanen, S. *Science* **1994**, *263*, 380.

(104) Chorev, M.; Goodman, M. *Acc. Chem. Res*. **1996**, *26*, 266.

(105) Tamilarasu, N.; Huq, I.; Rana, T. M. *J. Am. Chem. Soc.* **1999**, *121*, 1597.

(106) Bobde, V.; Sasidhar, Y. U.; Durani, S. *Int. J. Peptide Protein Res*. **1994**, *43*, 209.

(107) Aravinda, S.; Shamala, N.; Desiraju, S.; Balaram, P. *Chem. Commun.* **2004**, 2454.

Chapter 2 Molecular Modeling of Oligoureas

2.1 Introduction of molecular modeling

Computation is a common starting point for molecular design. To gain deeper insight into the feasibility of oligoureas as peptide mimics, molecular modeling was applied to provide information about the possible secondary structures of the target oligoureas.

Molecular modeling is a term used to describe the study of the behavior of molecules and molecular systems.[1] Both quantum mechanics and molecular mechanics principles can be used in molecular modeling depending on the specific problem to be solved.

Quantum mechanics has been used to investigate a wide variety of chemical problems including: the geometry of molecules (bond lengths, bond angles, dihedral angles); the energies of both molecules and transition states; chemical reactivity of molecules; IR, UV, NMR spectra of molecules; the interactions between substrates and enzymes; the physical properties of substances.[2] Molecular mechanics is more applicable to the geometries of molecules and the investigation of competing conformations of molecules. Calculations with molecular mechanics scale more economically with molecular size than quantum calculations, thus large molecules are tractable with molecular mechanics. Molecular mechanics logically was chosen to investigate possible low-energy conformations of the oligoureas in this work.

In MM, a molecule is viewed as a collection of spheres (atoms) held together by springs (bonds). The energy of the molecule changes if the geometry of the molecule is changed, i.e. the springs being stretched or bent away from their "natural" positions and the balls being pushed too closely together. [2]

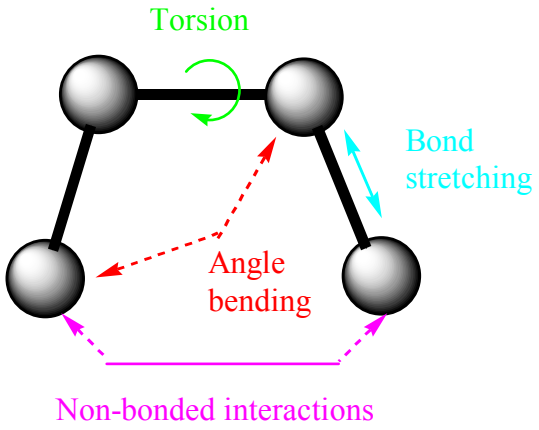


Figure 2.1 A molecule model in molecular mechanics[3]

Mathematically the energy of a molecule can be expressed as a function of its resistance toward bond stretching, bond bending, bond twisting and atom crowding.

$$E_{total} = \sum_{bonds} E_{stretch} + \sum_{angles} E_{bend} + \sum_{dihedrals} E_{torsion} + \sum_{pairs} E_{nonbond}$$

The energy, together with the parameters in it, is called a force field. Consequentially MM methods are sometimes called force field methods. [2]

Over the years many different kinds of force fields have been developed. Although all the force fields have the four basic energy terms, the mathematical expressions vary from one force field to another because different considerations were made during the process of developing the force fields. Still additional energy terms are added to account for other kinds of interactions and deformations in order to improve the accuracy of the mechanical model.[3]

2.2 Computation of oligoureas

Molecular modeling was used to calculate the geometries and search the conformations of the target oligoureas. The calculations were realized by MacroModel, a force field based molecular modeling program developed by Schrodinger Inc.[4] To perform the conformation searches for the target oligoureas, a suitable force field has to be chosen first. In this work, AMBER force field was selected.

2.2.1 AMBER force field

Amber is probably the most popular force field for proteins and nucleic acids modeling. Till now, two generations of AMBER force fields have been developed by the Kollman research group. The energy equations of the first (A) and second (B) generations AMBER force fields are shown below.[5,6]

$$E_{total} = \sum_{bonds} K_r (r - r_{eq}) + \sum_{angles} K_\theta (\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j} [\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}] + \sum_{H-bonds} [\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}}] \quad (A)$$

$$E_{total} = \sum_{bonds} K_r (r - r_{eq}) + \sum_{angles} K_\theta (\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j} [\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}] \quad (B)$$

(*R, distance; q, charge; A, B, C, D, coefficients; ε, dielectric distance.*)

The difference between the two energy equations is that in the first generation equation, a 10-12 function is included to account for hydrogen bonding, while in the second generation equation, this term is incorporated into the fourth energy term because of the development of a new charge model and new van der Waals parameters.[6] The parameters in the energy terms in both equations are first obtained from experimental data (microwave, neutron diffraction, NMR, X-ray diffraction) as well as molecular mechanical/*ab initio* calculations, and then refined with molecular mechanical studies on the structures and energies of model compounds. The second generation force field has improved accuracy compared with the first generation because of the use of new models and the introduction of new parameters.[6]

2.2.2 Solvation effect[7]

In molecular modeling, the effect of solvent must be considered. To account for the effects of solvents, a solvent is treated as a statistical continuum.[8] The free energy of solvation (G_{sol}) consists of a solvent-solvent cavity term (G_{cav}), a solute-solvent van der Waals term (G_{vdW}), and a solute-solvent electrostatic polarization term (G_{pol})**:**

$$G_{sol} = G_{cav} + G_{vdW} + G_{pol}$$

For the saturated hydrocarbons in water, Gsol is linearly related to the atomistic solvent-accessible surface area (SA),

$$G_{cav} + G_{vdW} = \sum \sigma_k SA_k$$

SA_k is the total solvent-accessible surface area of atoms of type k and σ_k is an empirical atomic solvation parameter.

For G_{pol}, it can be expressed by the generalized Born (GB) equation.[9]

$$Gpol = -166(1-\frac{1}{\varepsilon})\sum_{i=1}^{n}\sum_{j=1}^{n}\frac{q_i q_j}{f_{GB}}$$

(ε, dielectric constant; q, charge; f_{GB}, a function of distance and radii)

2.2.3 Conformational search-Monte Carlo Multiple Minimum (MCMM)

A flexible molecule has numerous conformations theoretically, but only certain conformation or conformations are most populated. To find a set of low-energy conformers, a conformational search is usually performed. The conformational search process involves three general steps: the generation of a new structure, minimization of the structure, and determination of the suitability of the structure.

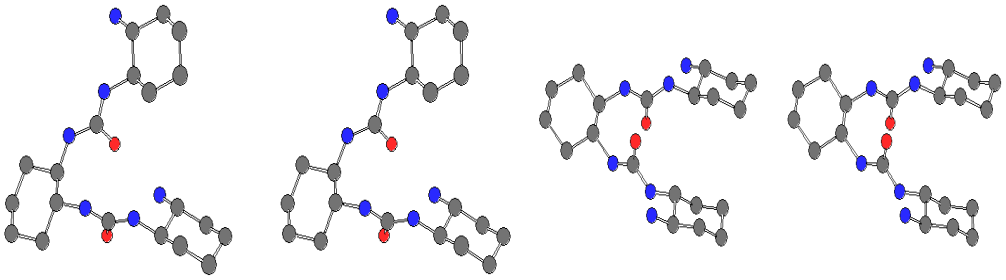
Monte Carlo Multiple Minimum (MCMM) is one of the conformational search methods of MacroModel. An MCMM conformational search is a repeat of multiple Monte Carlo steps. It begins with an intelligently chosen starting structure for a target molecule, this structure is then subjected to energy minimization; an optimized conformer is produced after the minimization, and then an energy and duplication test is run for the resulting conformer; if it passes the test, then it is stored as a unique conformer, otherwise it is rejected. The process is repeated by generating a new structure based on a random algorithm as a new starting point, running energy minimization to produce an optimized new conformer, testing energy and possible duplication, retaining or rejecting the resulting new conformer. The search is terminated when all the possible conformers within the set energy window are found.[10, 11]

2.3 Results

Conformational search with MacroModel was performed for both homochiral and heterochiral C_2-symmetric oligoureas. D-amino acids incorporated in a chain mainly made of L-amino acids are known to affect the structure of the resulting peptide. To test the effect of heterochiral units, calculations were done for heterochiral oligoureas. The results are shown below.

2.3.1 Conformation search for all R and RSR triureas based on 1,2-diaminocyclohexane (DACH)

Conformational search for both global energy-minimum conformation and local minima was performed for the all R DACH triurea. Using Amber* force field and the water solvent continuum, Monte Carlo-Multiple Minimum conformational searches (2000 steps) found 86 unique conformations within a window of 20 kJ/mol (2000 max iterations for each minimization). Among the 86 conformers, 31 have the urea carbonyls pointing in the same direction or nearly the same direction, and the rest (including the global minimum (**Figure 2.2 A**)) have the urea carbonyls either pointing in opposite directions or one is perpendicular to the other. Most of the conformers are extended (**Figure 2.2 B**) (they are either flat or only with one end residue slightly higher than the rest), for those having turns, well-defined helices were found 5 times.

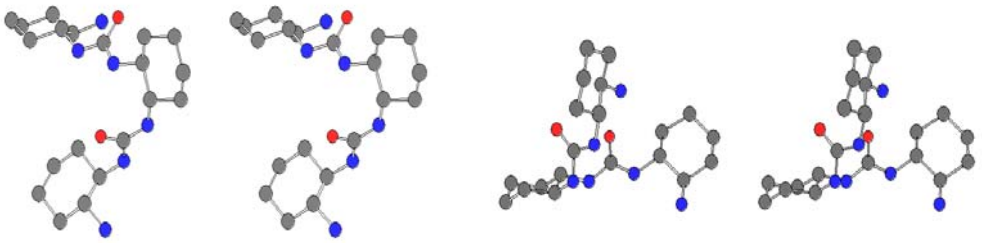


A. Global minimum of all R DACH triurea

B. An extended structure (carbonyls pointing in opposite directions)

Figure 2.2 Stereodigram of some calculated conformers of all R DACH triurea. To view the stereoimages, use the cross-eyed method instead of the wall-eyed method.[12] The following images should be viewed with the same method.

The same MCMM conformational search (2000 steps) for RSR DACH triurea found 159 structures. Half of the conformers have both urea carbonyls pointing in opposite directions and the other half almost in the same direction. The first three conformers (the global minimum (**Figure 2.3 A**) and the two lowest energy conformers) have both carbonyls in opposite directions, and the next five low energy conformers have both carbonyls pointing in the same direction (**Figure 2.3 B**). Neither structures is extended, both have the "turn" in common. If this turn were extended infinitely, it would define a helix consisting of periods of ~ 3.0 residues.



A. Global minimum (carbonyls pointing in oppisite directions)

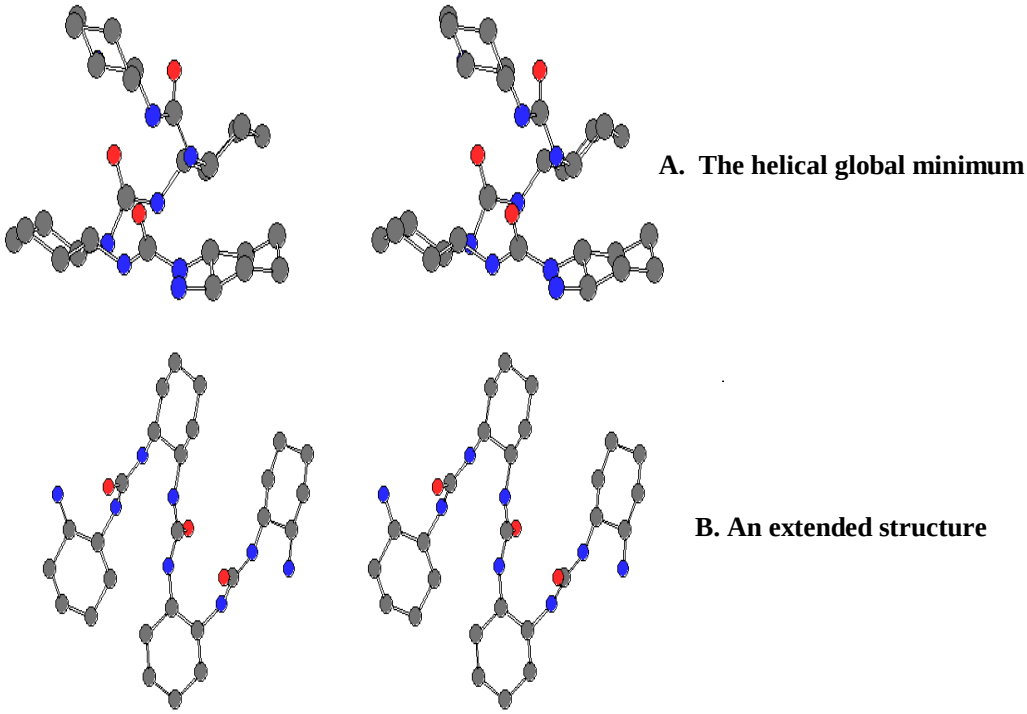
B. A conformer with carbonyls pointing in the same direction

Figure 2.3 Stereodiagram of some calculated conformations of RSR DACH Triurea

2.3.2 Conformation search for all R DACH tetraurea

The same calculation as above in section 2.3.1 was done for the all R DACH tetraurea. The MCMM conformational search found 152 unique conformers within a window of 20 kJ/mol (2000 max iterations for minimization). Among the 152 conformers, about 60 (**Figure 2.4 B**) are extended or near extended. The extended structures have the urea carbonyls pointing in opposite

directions; while the near extended structures have some kind of bend: for example, three residues in the same plane, while the fourth one is slightly above the plane, or the middle two residues in the same plane, while the first and fourth ones bend over to an extent. The rest have some kind of turn in the structure, with 20 well-defined helices or near well-defined helices. The global minimum has some helix-like structure (**Figure 2.4 A**). For the DACH tetraurea, the calculation predicts that extended structures should be more populated than the helix-like structures.



A. The helical global minimum

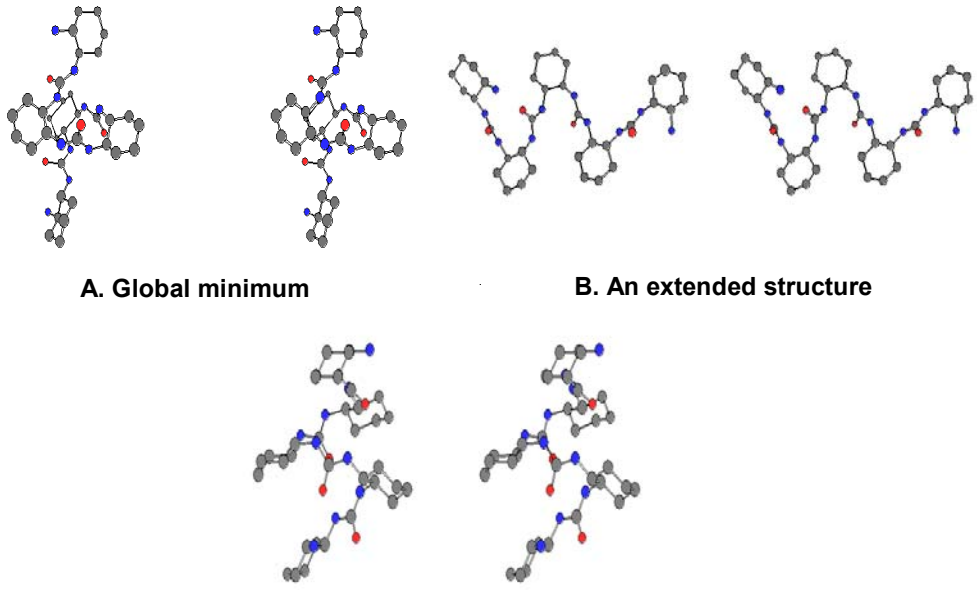
B. An extended structure

Figure 2.4 Stereodigram of some calculated conformations for all R DACH tetraurea

2.3.3 Conformation search for DACH pentaureas

An MCMM conformational search for the all R DACH pentaurea found 165 unique conformations. The first four conformers (the global minimum (**Figure 2.5 A**) and the three lowest energy conformers) have structures similar to the global minimum, which has the first two residues at the same plane, and the third residue acts as a bridge to dispose the fourth and fifth residues above the first three. This structure is folded to some degree but is not a well defined helix. Then the fifth to eighth conformers are better defined helices (**Figure 2.5 C**). For

the remaining structures, fully extended structures with all the urea carbonyls pointing in the opposite directions were not found, but extended structures with 4 residues at the same plane while the fifth one tilted a little bit were observed 40 times (**Figure 2.5 B**). Helices with the first three or four residues in position while the other residues fraying to some point were found about 50 times. The rest show turns, bends and zigzags. The calculation predicts a mixture of extended and helical conformations for the all R DACH pentaurea. The helical structure is likely the global minimum, but structures possessing extended regions appear to be entropically favored.



A. Global minimum **B. An extended structure**

C. A helix-like structure

Figure 2.5 Stereodiagram of some calculated conformations of all R DACH Pentaurea

For RSRSR DACH pentaurea, MCMM conformational search (7500 steps) found 77 unique conformations. Among the 77 conformers, 6 are not helix like, all the other 71 conformers are left-handed helices (**Figure 2.6**). The calculation strongly suggests a helical conformation for alternate RS DACH pentaurea.

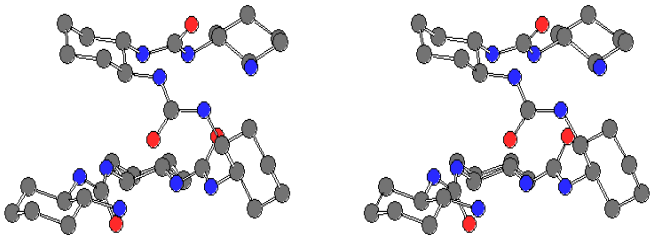
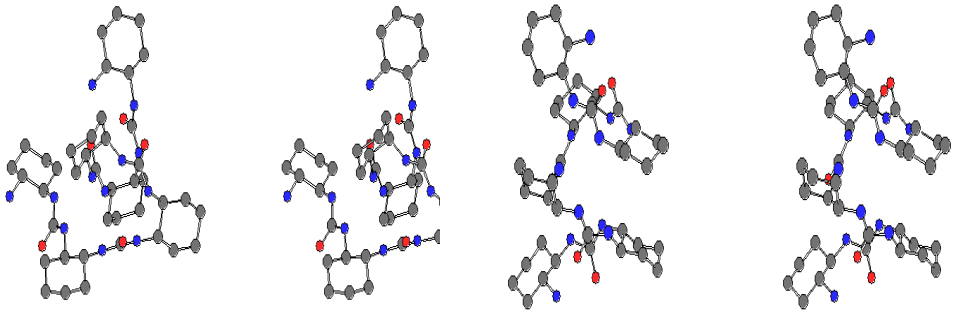


Figure 2.6 Stereodigram of the global minimum of alternate RS DACH pentaurea

A similar conformational search was done for RRSRR pentaurea. The program found 155 structures for this pentaurea. The first three structures (the global minimum (**Figure 2.7 A**) and the two conformers with second lowest energy) are neither extended nor well-defined helix, but the heterochiral unit did introduce a turn in the conformation. Structures from 4 to 7 are more helix like (**Figure 2.7 B**). The rest are more or less like the global minimum, and fully extended structure was not observed.



A. Global minimum **B. A helix-like structure**

Figure 2.7 Stereodiagram of some calculated conformations of RRSRR DACH pentaurea

2.3.4 Conformation search for all R DACH hexaurea

An MCMM conformational search for the all R DACH hexaurea found 55 unique conformations. Most of the conformers (including the global minimum) are left-handed helices with fraying at the end one or two residues (**Figure 2.8**), fully extended structures with neighboring urea carbonyls pointing in opposite (one up, the next one down) directions were not found, but near extended structures with 4 residues in one plane while the fifth and sixth ones above the plane were found 14 times. Other non helix-like structures showed turns combined

with extended parts. Like pentaurea based on DACH, the hexaurea is predicted to have some folded structure but still associated with ambiguity.

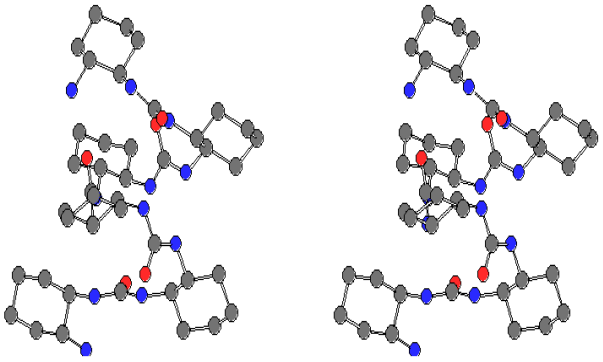


Figure 2.8 Stereodiagram of the helical structure of all R DACH hexaurea

2.3.5 Conformation search for DACH heptaureas

For DACH heptaureas, calculations were carried out for *bis*-*N*-acetyl-($\mathbf{1}_R$)$_7$, and *bis*-*N*-acetyl-($\mathbf{1}_S$–$\mathbf{1}_R$)$_3$–$\mathbf{1}_S$, analogs of *N*-acetylmethyl ester of Ala$_7$.

Performing Monte Carlo-Multiple Minimum conformational searches for a global energy-minimum conformation of *bis*-*N*-acetyl-($\mathbf{1}_R$)$_7$ with the force field Amber* in MacroModel 8.1 resulted in an energetic preference for a right-handed helix. The $CHCl_3$ continuum dielectric field gave more robust folded structure, but otherwise the results were similar to the calculations using the water solvent continuum. These computations were initiated from high-energy extended conformations with all the urea carbonyls pointing in the same direction. Within a window of 50 kJ/mol (max 2000 iterations for minimization) the computation found 632 structures with most of the conformers alternating the direction of the urea carbonyls. The first three structures (the global minimum and the two lowest energy conformers) were right-handed helices (**Figure 2.9 B**), the fifth structure and beyond were basically extended as in **Figure 2.9 A** (these extended regions were mixed with hydrogen bonded loops and turns). Even though the helical structures are global energy minima, calculation actually predicts a global extended conformation for ($\mathbf{1}_R$)$_7$. As the concentration increases the extended conformation should be even more favored due to inter-chain hydrogen bonding in a manner similar to the β-sheet type aggregation of intractable peptides that favor an extended conformation.[13-15]

An analogous calculation for *bis*-*N*-acetyl-(**1**$_S$–**1**$_R$)$_3$–**1**$_S$, an isostructural heptaurea with residues of alternating chirality, found only 329 local minima within the same 50 kJ/mol energy window. The ~150 lowest-energy conformers were helices instead of extended structure! The higher energy conformers were all kinked chains that turned to the left then to the right along with some portion of the chain extended. This calculation predicts a folded structure for the alternating RS oligomer.

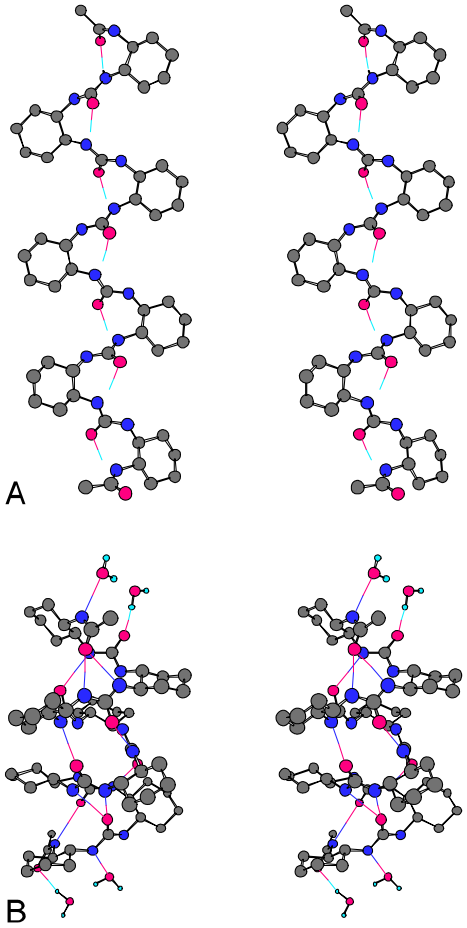


Figure 2.9 Stereodiagram of calculated conformations of A: (1R)$_7$ and B: (1S1R)$_3$1S

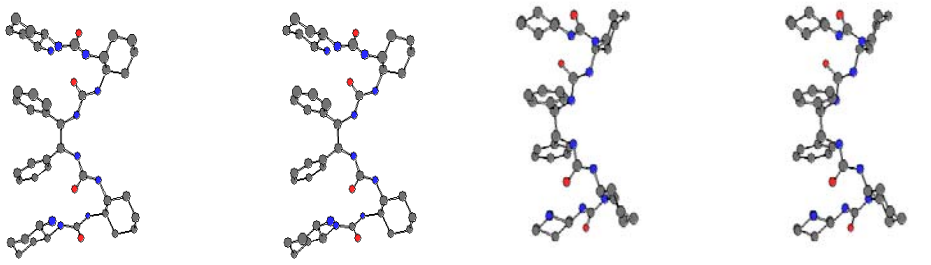
Taken together, these calculations predict that the chain of alternate chiral residues should rest in a helical global conformation whereas more conformational ambiguity is associated with the dynamics of the homochiral chain. The minimal effect of solvent dielectric suggests that interactions of closely-spaced bond dipoles play a large part in the control of conformation on top of and in addition to intramolecular hydrogen bonding in the helical

conformation. Calculations with derivatives of $\mathbf{2}_n$ reach the same conclusion predicting that the residues can be changed without a drastic perturbation to the global conformation.

The less chiral chain is predicted to prefer the more dissymmetric conformation, if one accepts the notion that dissymmetry can be quantified.[16-22] The fact that D-residues in L-chain peptides induce turns coincides with these predictions;[23-40] any helix is composed of a string of sequential, specific local turns. Thus, calculation predicts that these simple C_2-symmetric oligomers have much in common with peptide conformation.

2.3.6 Conformation search for all R pentaurea based on both DACH and 1,2-diphenylethylenediamine (DPEDA)

To investigate the effect of monomers, a conformational search was done for a heterostructural pentaurea based on both DACH and DPEDA. 74 conformers were found for all R pentaurea from the MCMM conformations search. The first 5 (the global minimum (**Figure 2.10 A**) and the 4 lowest energy conformers) conformers are all extended or near extended, the remaining 70 conformers include near 20 extended structures, 18 structures with some helicity (but not well-defined helices) (**Figure 2.10 B**), and the rest normally have four residues forming extended structure while the fifth one being above or under the chain.



A. Global minimum **B. A structure with some helicity**

Figure 2.10 Stereodiagram of some calculated stuctures for all R pentaurea $DACH_2$-DPEDA-$DACH_2$

2.3.7 Conformation search for a pentaurea with achiral monomer in the middle

Furthermore, the effect of achiral monomers is examined by calculation. MCMM conformational search was performed for a DACH pentaurea with ethylenediamine (EDA) in the middle.

The MCMM conformational search for this pentaurea found 225 unique conformations, the majority of the conformers (including the global energy-minimum) are left-handed helices, only a few conformers have disordered structure.

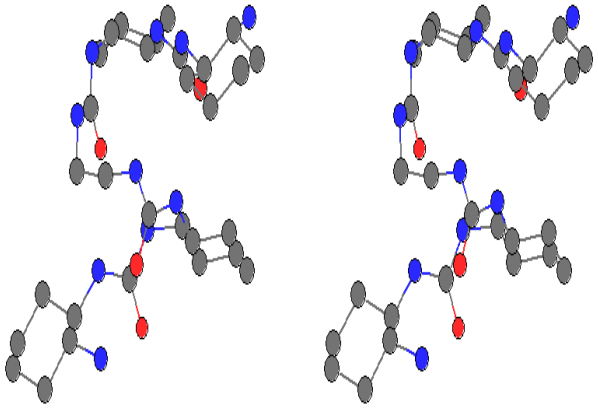


Figure 2.11 Sterodiagram of the global minimum of all R pentaure $DACH_2$-EDA-$DACH_2$.

2.3.8 Dihedral angles of four nitrogen atoms on adjacent diamine units as conformational parameters

A careful examination of the dihedral angles (**Figure 2.12**) between the four nitrogen atoms on adjacent diamine units for the calculated conformations found that: for extended structures, large angles (over 120°, all positive or negative) were associated; and for helical structures, small angles (less than 50°) were associated. For example, for the extended structure for all R DACH tetraurea (**Figure 2.4 B**), the dihedral angles are 167.2°, 165.6° and 154.1° respectively from left to right; and for the near helical structure for all R DACH hexaurea (**Figure 2.8**), the dihedral angles are 165.2°, -13.6°, -22.3° and -39.8° respectively from bottom to top. The nitrogen atoms dihedral angles might be used as criteria for conformation determination for the target oligoureas.

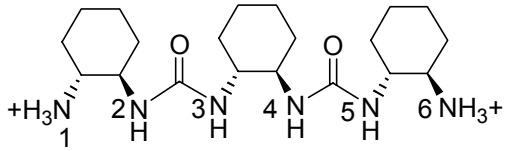


Figure 2.12 All R DACH triurea as an example of dihedral angles measurement. Dihedral angles are measured for N1-N2-N3-N4, N3-N4-N5-N6.

2.4 Conclusion

To gain deeper insight into the feasibility of oligoureas as peptide mimics, conformational searches were performed for different oligoureas. The calculation for homochiral oligoureas based on DACH shows that the triurea prefers to have extended structure; and more ambiguity is associated with tetraurea (extended structure and helix-like structure have similar population); pentaurea prefers folded structure over extended structure; and for hexaurea, folded structure is dominant; while for acetylated heptaurea, although the global minima are helices, the extended structure is more populated. For the alternate chiral oligoureas, folded structure is preferred even for short chains like RSR triurea, and for the alternate RS pentaurea and heptaurea, helix is the dominant conformation. With the integration of a DPEDA monomer in the DACH chain, the conformation preference of the pentaurea is affected possibly because of the π interaction. Also achiral residues play a role in the conformation control of these oligoureas, a DACH pentaurea with EDA monomer in the middle was calculated to form a helix. In general, the calculations indicate that the conformational preference of the target chiral oligoureas is similar to peptides in that extended and helical structures are possible. Furthermore structural biases exist for these conformational families. Selection of these families of conformations could be accomplished by incorporating side chains or by changing the absolute chirality of the residues in the chain. These ideas will be pursued in the next chapters.

2.5 References

(1) Leach, A. R. Molecular Modeling: Principles and Applications; 2nd Edition, 2001.

(2) Lewars, E. *Computational Chemistry: Introduction to the Theory and Applications of Molecular and Quantum Mechanics;* Kluwer Academic Publishers, 2003.

(3) http://cmm.cit.nih.gov/modeling/guide_documents/molecular_mechanics_document.html.

(4) MacroModel 8.1 User Manual.

(5) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S. Jr.; Weiner, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 765.

(6) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M. Jr.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179.

(7) Still, W. C.; Tempczyk, A.; Hawley R. C.; Hendrickson, T. *J. Am. Chem.* Soc**. 1990**, *112***,** 6127.

(8) Eisenberg, D.; McLachlan, A. D. *Nature* **1986**, *319*, 199.

(9) Kozaki, T.; Morihashi, K.; Kikuchi, O. *J. Am. Chem. Soc*. **1989**, *111*, 1547.

(10) Saunders, M.; Houk, K. N.; Wu, Y. D.; Still, W. C.; Lipton, M.; Chang, G.; Guidal, W. C. *J. Am. Chem. Soc.* **1990**, *112,* 1419.

(11) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989,** *111***,** 4379.

(12) http://en.wikipedia.org/wiki/Autostereogram

(13) Mayo, K. H.; Ilyina, E.; Park, H. *Protein Science* **1996,** *5*, 1301.

(14) Thirumalai, D.; Klimov, D. K.; Dima, R. I. *Curr. Opin. Struct. Biol.* **2003,** *13*, 1.

(15) Richardson, J. S.; Richardson, D. C. *Proc. Natl. Acad. Sci. USA* **2002,** *99*, 2754.

(16) Zabrodsky, H.; Peleg, S.; Avnir, D. *IEEE Transactions on Pattern Analysis and Machine Intelligence* **1995,** *17*, 1154.

(17) Zabrodsky, H.; Avnir, D. *J. Am. Chem. Soc.* **1995,** *117*, 462.

(18) Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1993,** *115*, 11656.

(19) Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1993,** *115*, 8278.

(20) Buda, A. B.; Derheyde, T. A.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1992,** *31*, 989.

(21) Buda, A. B.; Mislow, K. *J. Am. Chem. Soc.* **1992,** *114*, 6006.

(22) Heyde, T.; Buda, A. B.; Mislow, K. *J. Math. Chem.* **1991,** *6*, 255.

(23) Aravinda, S.; Shamala, N.; Desiraju, S.; Balaram, P. *Chem. Commun.* **2002**, 2454.

(24) Bobde, V.; Sasidhar, Y. U.; Durani, S. *Int. J. Pept. Protein Res.* **1994,** *43*, 209.

(25) Clark, T. D.; Buehler, L. K.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1998,** *120*, 651.

(26) Convert, O.; Duplaa, H.; Lavielle, S.; Chassaing, G. *Neuropeptides* **1991,** *19*, 259.

(27) Ehrlich, A.; Heyne, H.-U.; Winter, R. D.; Beyermann, M.; Hanka Haber; Carpino, L. A.; Bienert, M. *J. Org. Chem.* **1996,** *61*, 8831.

(28) Formaggio, F.; Bettio, A.; Moretto, V.; Crisma, M.; Toniolo, C.; Broxterman, Q. B. *J. Pept. Sci.* **2003,** *9*, 461.

(29) Hong, S. Y.; Oh, J. E.; Lee, K. H. *Biochem. Pharmacol.* **1999,** *58*, 1775.

(30) Imperiali, B.; Fisher, S. L.; Moats, R. A.; Prins, T. J. *J. Am. Chem. Soc.* **1992,** *114*, 3182.

(31) Kiyota, T.; Yanagida, R.; Oka, M.; Miyoshi, M.; Lee, S.; Sugihara, G. *Bull. Chem. Soc. Jpn.* **2000,** *73*, 2363.

(32) Krause, E.; Beyermann, M.; Fabian, H.; Dathe, M.; Rothemund, S.; Bienert, M. *Int. J. Pept. Protein Res.* **1996,** *48*, 559.

(33) Krause, E.; Rothemund, S.; Beyermann, M.; Bienert, M. *Anal. Chim. Acta* **1997,** *352*, 365.

(34) Krause, E.; Bienert, M.; Schmieder, P.; Wenschuh, H. *J. Am. Chem. Soc.* **2000,** *122*, 4865.

(35) Lee, D. L.; Powers, J. P. S.; Pflegerl, K.; Vasil, M. L.; Hancock, R. E. W.; Hodges, R. S. *J. Pept. Res.* **2004,** *63*, 69.

(36) Maeda, M.; Melnyk, R. A.; Partridge, A. W.; Liu, L. P.; Deber, C. M. *Biopolymers* **2003,** *71*, 77.

(37) Mitchell, J. B. O.; Smith, J. *Proteins: Struct., Funct., Genet.* **2003,** *50*, 563.

(38) Rothemund, S.; Krause, E.; Beyermann, M.; Dathe, M.; Bienert, M.; Hodges, R. S.; Sykes, B. D.; Sonnichsen, F. D. *Peptide Research* **1996,** *9*, 79.

(39) Weisshoff, H.; Prasang, C.; Henklein, P.; Frommel, C.; Zschunke, A.; Mugge, C. *Eur. J. Biochem.* **1999,** *259*, 776.

(40) Wieprecht, T.; Dathe, M.; Schumann, M.; Krause, E.; Beyermann, M.; Bienert, M. *Biochemistry* **1996,** *35*, 10844.

Chapter 3 Conformational Study of the Oligoureas

3.1 Overview

Although the molecular modeling in the previous chapter showed that the target oligoureas could form both helix and extended structures conditionally, analogous to naturally occurring peptides, this prediction had to be experimentally verified. Still other aspects of these oligoureas need to be investigated. Cooperative behavior is one of these.[1] Cooperative behavior is common in higher order structures such as the secondary and tertiary structures of proteins and RNA, furthermore cooperativity may be essential for sophisticated chemical and biological functions of these biopolymers. Investigating what is the minimum chain length for the oligoureas to fold, how increasing the chain length would facilitate the formation and stability of the secondary structures is one goal of this project. Studying the effect of other factors such as solvent and temperature on the conformation is another.

All the possible foldamer-specific characterization techniques including infrared spectroscopy (IR), ultraviolet-visible (UV-vis) spectroscopy, X-ray crystallography, NMR (both 1D and 2D) spectroscopy and *C*ircular *D*ichroism (CD) can be used to fulfill the conformational study on the oligoureas. Among them, X-ray crystallography, NMR and CD are the three major tools.

3.2 Solid state conformation of some oligoureas

Crystallography is probably the most accurate method for structure determination. X-ray crystallography was used to study the conformation of these oligoureas in the solid state. But to obtain the conformation of the solid state, crystals have to be grown first. The process of crystal growth of macromolecules is quite complicated and not fully understood yet, but ideally, the crystallization process can be divided into two steps: 1. a nucleation process and 2. crystal growth. A lot of experience and useful methods have been accumulated.[2] With enough pure material, there is a good chance of growing X-ray quality crystals. So far, X-ray quality crystals for several oligoureas have been obtained, and the crystal structures have been determined successfully.

Oligoureas with chains longer than five residues of monomeric unit **1** or **2** did not produce diffraction-quality crystals. However, the crystal structures of various diureas, triureas and a pentaurea were informative, especially in light of the calculations presented above. Both helices

and extended structures were detected in the solid state, the short homochiral oligoureas tended to form extended structure while the heterochiral ones preferred the helix.

3.2.1 Solid state conformation of homochiral oligoureas

For the homochiral oligoureas, the crystal structures of some Boc (t-butoxycarbonyl) protected diureas, Boc protected and deprotected triureas, and **a** deprotected pentaurea have been obtained so far. The common feature of these crystals except for one is the directionality of the urea carbonyl dipoles being opposite (one up, the next down) at each residue for all the crystal structures. The solid state conformation of these homochiral oligoureas appeared to reflect the conformational propensities predicted by the calculations in chapter 2, they all formed extended beta-like conformation.

For Boc protected oligoureas **1**, **2**, and **3**, no solvent molecules participate in the hydrogen bonding array. One oligourea molecule is stacked on top of the other in a near perfect hydrogen bonded array.

The crystal structure of all R DACH diurea (**1**) is shown in **Figure 3.1.** The oligourea molecules are held one top of the other by intermolecular hydrogen bonding between the NH of the carbamate of one molecule and the C=O of the carbamate of another molecule, the two carbonyls of the same diamine residue point in opposite directions.

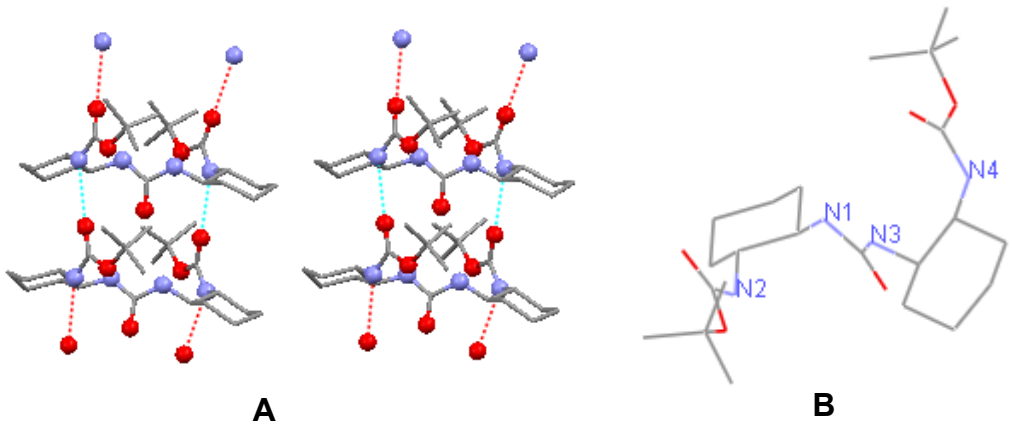


Figure 3.1 A. Stereodiagram of the crystal structure of Boc protected DACH diurea (1). To view the stereoimages, use the cross-eyed method instead of the wall-eyed method. The following images should be viewed with the same method. Hydrogen atoms are omitted for clarity. Oxygen and nitrogen atoms are displayed as red and blue spheres respectively. The dashed lines indicate hydrogen bonds found by the algorithm in Mercury 1.4 developed by the Cambridge Crystal Data Center 2001-2005, http://www.ccdc.cam.ac.uk/mercury/. Other crystal strucures in this chapter were produced by the same way. B. Structure of (1) and labeling of the N atoms.

The crystal structure of an all R thiourea dimer based on DACH (**2**) is shown in **Figure 3.2.** Still intermolecular hydrogen bonding holds the molecules together, but because of the elongated C=S bond, another hydrogen bonding molecular partner is observed, this is between the C=S of the thiourea of one molecule and the two NHs of the thiourea of another molecule. The C=S is pointing in the opposite direction from the carbamate C=O.

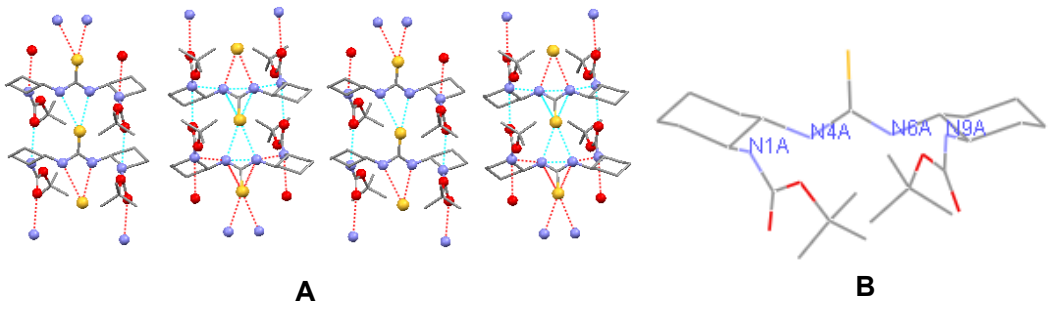


Figure 3.2 A. Stereodiagram of the crystal structure of a Boc protected DACH thiourea dimer (2); B. Structure of (2) and the labeling of N atoms.

The crystal structure of all R triurea based on both DACH and DPEDA (**3**) is shown in **Figure 3.3.** Three pairs of hydrogen bonding exist between every two oligoureas, the two carbonyls in every diamine residue point in opposite directions, the molecule forms an extended conformation.

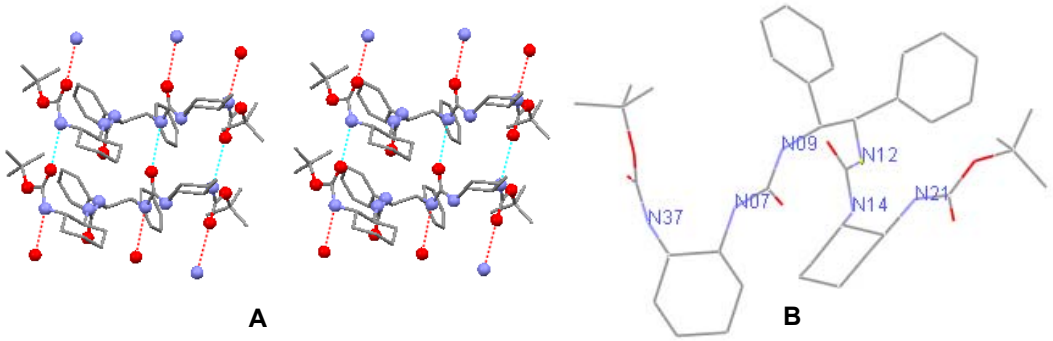


Figure 3.3 A. Stereodiagram of the crystal structure of Boc protected all R triurea based on DACH and DPEDA (3); B. Structure of (3) and labeling of N atoms.

For Boc protected DACH triurea (**4)**, the same stacking pattern as (**3)** exists. But one water molecule is associated with every three oligoureas, the water molecule acts as a bridge for neighboring oligoureas. The molecule is still extended. The crystal structure of (**4**) is shown in **Figure 3.4.**

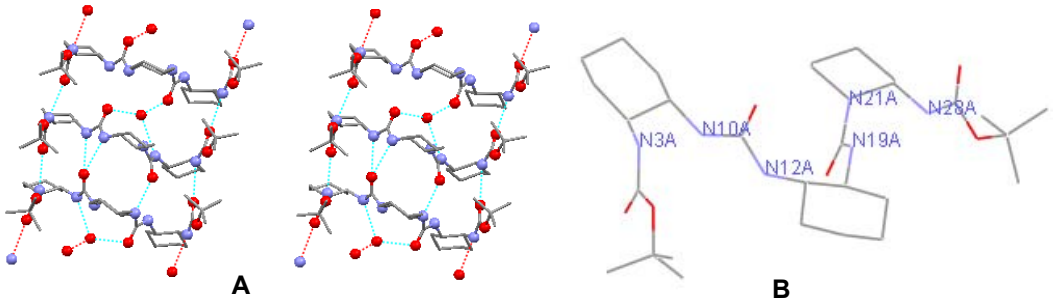


Figure 3.4 A. Stereodiagram of the crystal structure of Boc protected all S DACH triurea (4); B. Structure of (4) and labeling of N atoms

While for the deprotected oligoureas, the hydrogen bonding net is more complicated because of the participation of charge and solvent molecules. The crystal structure of all R DACH triurea with Boc removed (**5**) is shown in **Figure 3.5.** The chain molecules are not stacked one upon another any more because trifluoroacetate and methanol molecules are

involved in the hydrogen bonding, but it is obvious the deprotected triurea still has an extended structure with the two neighboring carbonyls pointing in the opposite directions.

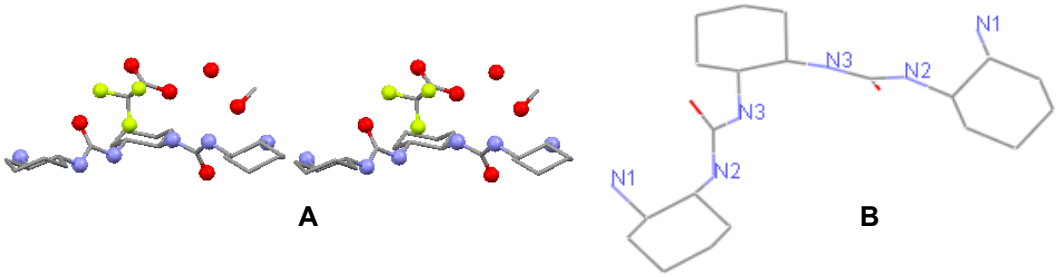


Figure 3.5 A. Stereodiagram of the crystal structure of deprotected DACH triurea (5); B. Structure of (5) and labeling of N atoms.

The crystal structure of all R pentaurea based on both DACH and DPEDA (**6)** with Boc removed is shown in **Figure 3.6.** Like triurea (**5**), this pentaurea also has a complicated hydrogen bonding net, both intermolecular and intramolecular hydrogen bondings were observed, one ammonium end forms Hydrogen bonding with the carbonyl on the same residue, and one molecule is stacked on the other with some slide, but this packing is 3-dimensional with trifluoroacetate and ethanol molecules involved. Nevertheless, the oligourea has extended structure with adjacent urea carbonyls in opposite directions.

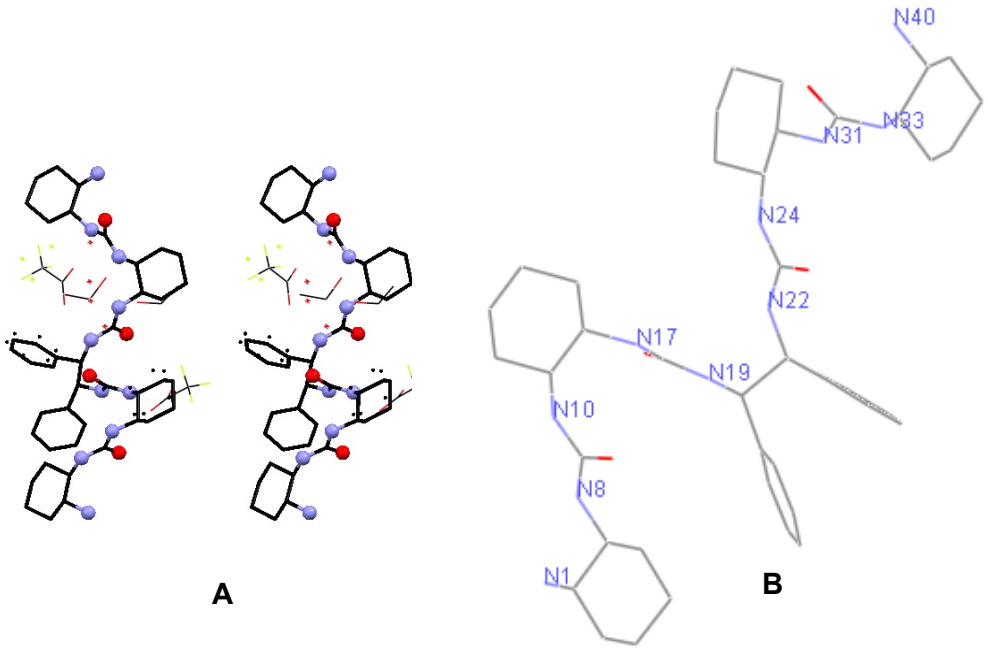


Figure 3.6 A. Stereodiagram of the crystal structure of deprotected all R pentaurea $(DACH)_2$-DPEDA-$(DACH)_2$ (6); B. Structure of (6) and labeling of N atoms.

The crystal structure of all R triurea DACH-DPEDA-DACH with Boc removed (**7)** is shown in **Figure 3.7.** In this crystal structure, the two carbonyls are not pointing at opposite directions. The whole molecule bends to an extent, but in general it looks more extended than helix.

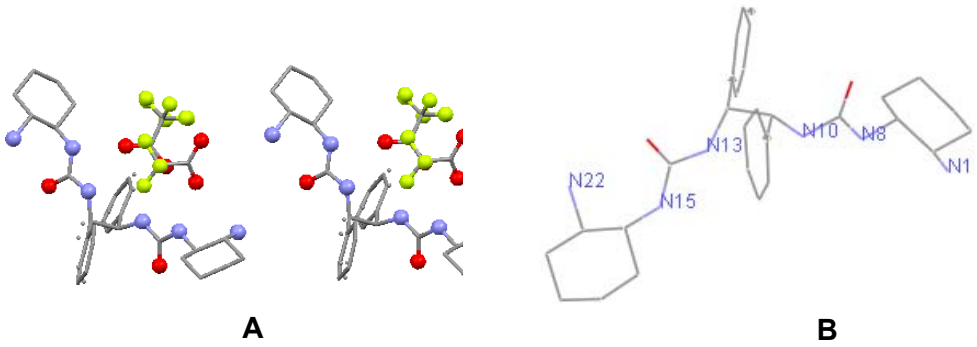


Figure 3.7 A. Stereodiagram of the crystal structure of deprotected all R triurea DACH-DPEDA-DACH (7); B. Structure of (7) and labeling of N atoms.

The dihedral angles of the backbone nitrogen atoms for homochiral oligourea are listed in **Table 3.1**. The absolute values of all the dihedral angles are larger than 120°, similar to the dihedral angles

of the extended structure of all R DACH tetraurea, and all the 7 oligoureas actually have extended structure as shown by the stereodiagrams.

Table 3.1 Dihedral angles of backbone nitrogen atoms for homochiral oligoureas **1** to **7**

Compound	Dihedral angles (°)			
1	175.17			
2	170.53			
3	-179.31		-152.95	
4	-151.50		-153.22	
5	156.26		156.26	
6	126.86	139.37	168.47	149.80
7	-138.01		-177.75	

3.2.2 Solid state conformation of heterochiral oligoureas

For the heterochiral oligoureas, two crystal structures were obtained. Compared with homochiral oligoureas, these molecules form helix structure instead of extended structure. Although the hydrogen bonding pattern is still complex due to the existence of charge and solvent molecules, the triureas complete ~one period of a helix, the N-atom termini ~coincided along the helical axes.

The crystal structure of alternate RS DACH triurea with Boc removed (**8)** is shown in **Figure 3.8**. In the molecule, the two carbonyls are pointing in the opposite directions, the end ammoniums lie on the same axis. The molecule is a left-handed helix.

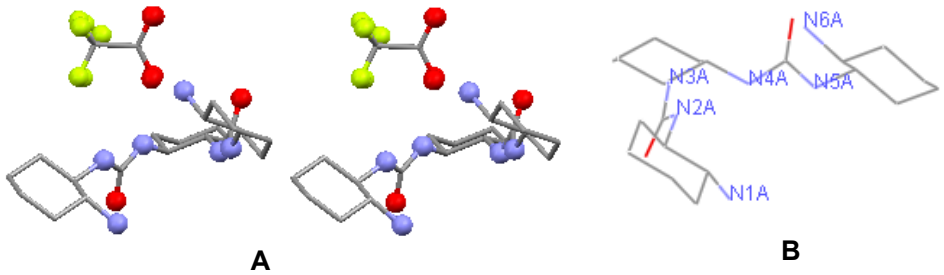


Figure 3.8 A. Stereodiagram of the crystal structure of RSR DACH triurea (8); B. Structure of (8) and labeling of N atoms.

The crystal structure of alternate RS triurea DACH-DPEDA-DACH with Boc removed (**9)** is shown in **Figure 3.9.** The molecule has a similar structure to (**8**), the carbonyls are at opposite directions, two ammonium ends stay on an axis. The compound forms a helix-like structure.

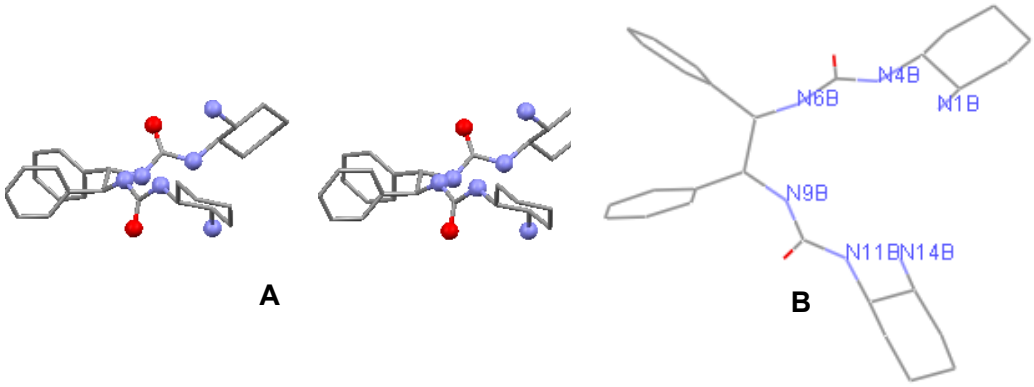


Figure 3.9 A. Stereodiagram of the crystal structure of RSR triurea DACH-DPEDA-DACH (9); B. Structure of (9) and labeling of N atoms.

The crystal structure of cyclohexylamine capped RSR DACH-DPEDA-DACH pentaurea (**10**) is shown in **Figure 3.10**. This molecule has a helical conformation with a methanol molecule inside the helix acting as a bridge connecting different diamine units, also intermolecular hydrogen bonding is formed between different helices.

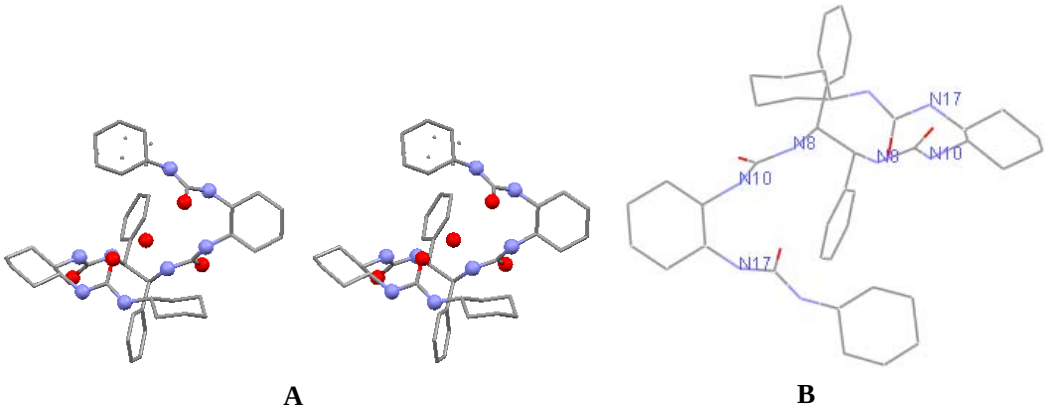


Figure 3.10 A. Stereodiagram of the crystal structure of cyclohexylamine capped RSR triurea DACH-DPEDA-DACH (10); B. Structure of (10) and labeling of N atoms.

The dihedral angles of the backbone nitrogen atoms for heterochiral oligoureas are listed in **Table 3.2**. All the dihedral angles are negative and the absolute values are less than 50°, they are similar to the dihedral angles of the helical structure of the all R DACH hexaurea.

Table 3.2 Dihedral angles of backbone nitrogen atoms for heterochiral oligoureas **8** to **10**

Compound	Dihedral angles (°)	
8	-39.63	-40.46
9	-43.03	-40.06
10	-27.18	-27.18

In general, the solid state conformation of both homostructural and heterostructural heterochiral oligoureas is in agreement with the conformational propensities predicted by the calculations in chapter 2.

3.3 Solution state conformation

Although crystallography is arguably the most definitive method for determining structure, X-ray quality crystals can not always be grown. Furthermore, solution phase conformations of various compounds may differ from the conformations adopted in the crystal structure. Solution phase structure determination is greatly facilitated by NMR spectroscopy, and, certainly for biological systems, circular dichroism (CD) has played an important role in structure determination. Both NMR and CD were applied to study the solution state conformation of these C_2-symmetric oligoureas.

3.3.1 Solution state conformation-2D NMR

NMR has to be used to study the conformation of oligoureas in solution. Amide proton exchange (NH/ND) has long been used to study conformational stability of peptides and proteins,[3, 4] formation of a stable secondary conformation leads to the slowdown of the NH/ND exchange rate, and this should be the case for oligourea as well. The NH/ND exchange rate of longer oligoureas relative to shorter ones would tell if the longer ones adopt stable intramolecularly hydrogen-bonded folding patterns. Also, variable temperature (VT) NMR would be very useful. The chemical shift change of the amide NH proton with temperature could produce coefficients ($-\Delta\delta/\Delta T$) for each NH proton in different oligoureas. From the temperature coefficient, one may be able to obtain qualitative and perhaps quantitative information on the population of the hydrogen-bonded NH in each oligourea.[5, 6] Two-dimensional NMR methods

such as COSY, TOCSY, NOESY and ROESY should give clues of the spatial relations between specific residues. This type of information should further lead to the knowledge of conformation. Furthermore, NMR titration of molecular hosts (oligoureas) with molecular guests such as ammonium phosphate would disclose the interactions between them.

Obtaining good NMR data for distance analysis to unambiguously determine the preferred conformation was riddled with difficulty. Solvents that sufficiently separated the NH peaks broadened them. Longer chains tended to give broad NH signals, but these long chains produced dynamic CD spectra indicative of folding whereas the shorter chains were less CD active. On top of this are the solubility issues and complications due to aggregation of protected derivatives in noncompetitive solvent. The conformation likely changed at the high concentrations in non-competitive solvent (compared with CD concentration) needed for the NMR studies due to intermolecular hydrogen bonding. Despite the difficulties, the NMR studies provided some clues about the conformation at NMR concentrations (3 mg /mL). To increase the chemical shift dispersion the diphenyl residue **2** (**Figure 3.11**) was included in the chain.

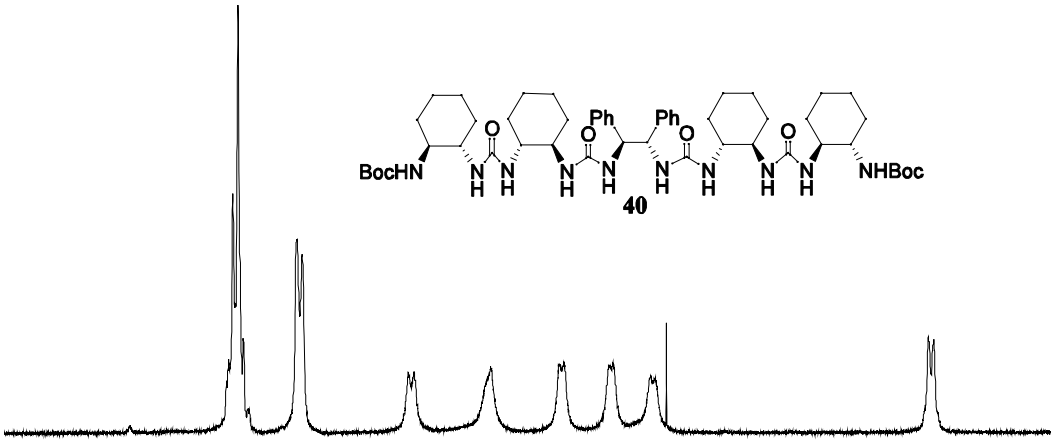


Figure 3.11 ^{1}H NMR of alternate RS pentaurea Boc-$(DACH)_2$-DPEDA-$(DACH)_2$-Boc. (only the downfield portion is shown.) All the urea NHs were well resolved.

2D NMR data (TOCSY and ROESY) were obtained for the homochiral pentaurea and heptaurea based on DACH and DPEDA. The data indicate that the homochiral heterostructural oligoureas likely adopt extended conformations because intra-residue cross peaks from dipolar relaxation were observed but no long-range inter residue cross peaks indicative of folded structure were observed (**Figure 3.12**). A 2D NMR study was also done for the alternate chiral heptaurea based on DACH and DPEDA at elevated temperatures (55 °C), the same results were

observed probably due to the thermal stability of the extended conformer in solution. Furthermore, the conformational invariance in the 2D ^{1}H NMR is not in conflict with the rich perturbable CD spectra if the increased concentration necessary for the 2D NMR promotes extended structure. This conclusion is also consistent with the prediction that the helical and extended conformation should be close in energy and thus rather conditional.

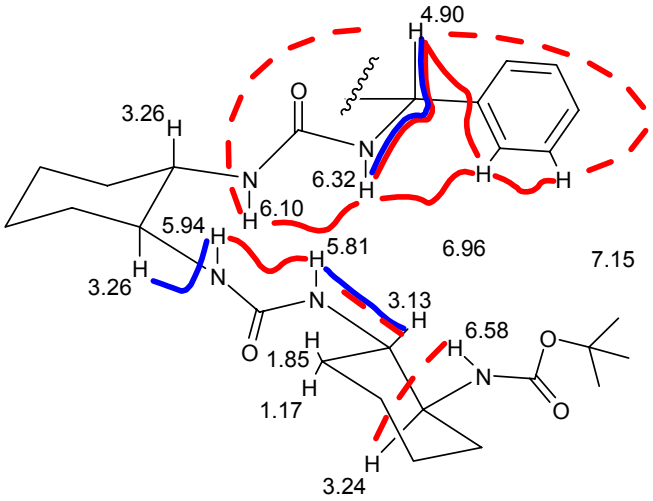


Figure 3.12 2D NMR (ROESY and TOCSY) for homochiral pentaurea Boc-(DACH)$_2$-DPEDA-(DACH)$_2$-Boc (only half of the molecule is shown here). The red curves indicate the ROESY correlations between hydrogen atoms in homochiral chain; the blue curves indicate TOCSY correlations; the chemical shifts of the alpha CH and the urea NH groups were assigned.

3.3.2 Conformation study-Circular dichroism

Circular dichroism (CD) is an empirical technique used to characterize chiral molecules and to probe the secondary structures of biomacromolecules. Since CD is a chiroptical method, the molecules under CD analysis have to possess optical activity. Ever since Holzwarth and Doty reported the first practical use of a CD spectropolarimeter to record the CD spectrum of an α-helix in 1965,[7] CD has been the standard practice in structure determination of peptides, proteins, nucleic acids, and oligo- and polysaccharides.[8-15] Chirality is the common property of all these biomolecules.[16]

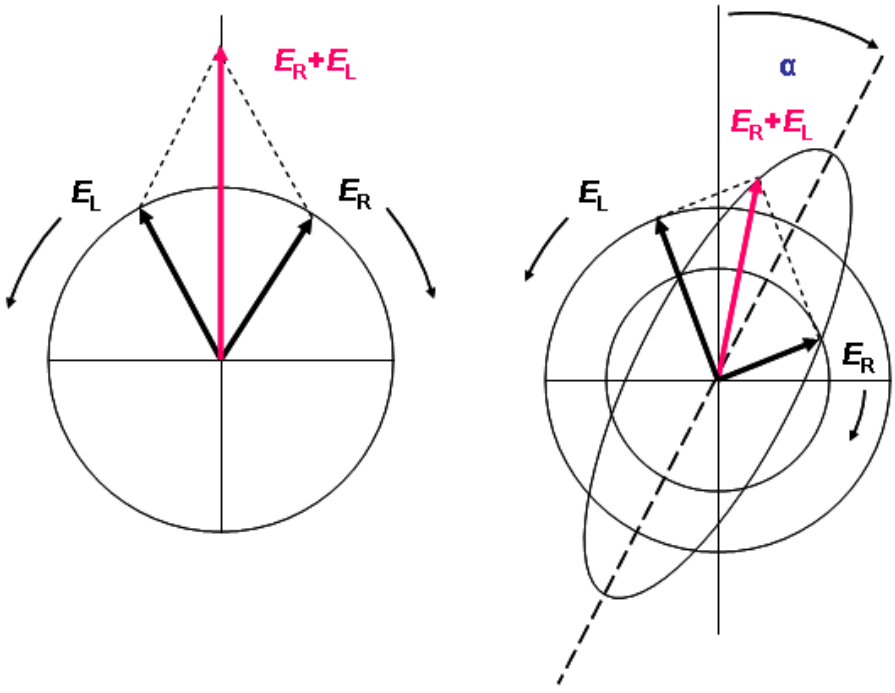
When linearly polarized light passes through an absorbing optically active sample, not only do the left and the right circularly polarized lights travel at different speeds, $C_L \neq C_R$, but also the two chiral electromaganetic phenomena are absorbed to a different extent, $\varepsilon_L \neq \varepsilon_R$. The difference $\Delta\varepsilon = \varepsilon_L - \varepsilon_R$, or $\Delta A = A_L - A_R$ is called Circular Dichroism.[17,18] According to Beer's law, the

difference in the absorption (ΔA) is proportional to the concentration of the sample (c), the path length (l), and the difference in molar absorptivity (Δε).

$$\Delta A = A_L - A_R = (\varepsilon_L - \varepsilon_R)lc = \Delta\varepsilon lc$$

In practice, the circular dichroic behavior of a molecule is measured as the ellipticity,θ, because, after absorption, the amplitude of the stronger absorbed component will be smaller than that of the less absorbed component. The consequence is that a projection of the resulting amplitude now yields an ellipse instead of a line (**Figure 3.13**). The ellipticity (often given in the units of millidegrees: mdeg) of a molecule is transformed at each wavelength into a value that depends upon the molecular mass, M (in g/mol) the concentration (g/L), and the pathlength, l (mm). The resultant values, known as the molar ellipticity, [θ], are those commonly reported in the literature for the CD of biomolecules.

$[\theta] = (\theta M)/cl.$[8]



(A) (B)

Figure 3.13 (A). Linearly polarized light can be resolved into left and right circularly polarized lights of equal amplitude and phase; (B). Different absoption of the left and right circularly polarized lights by a chiral sample leads to an ellipse.

Currently, increasing numbers of scientists have been applying CD to elucidate secondary structures in unnatural oligomers. The advantage is that from the CD signal, one can tell the existence of secondary structure. The disadvantage is that since there are no established spectroscopic signatures of secondary structures of unnatural oligomers, one can not really interpret the secondary structure by simply examining the CD curves.

CD is another powerful tool for the study of the solution phase conformation of oligoureas. The ellipticity (θ) difference between short and longer oligoureas should give information about the cooperativity behavior of oligoureas, and the ellipticity difference of oligourea systems with or without the presence of guest molecules would also tell the interactions between host and guest molecules. Also, CD can be used to study the effect of solvent and temperature on the conformation of the oligourea system.

3.3.2.1 Conformational study-Capping effect

First, the capping effect is studied by CD. Capping effect is the influence on the conformation of the molecule through removing the electrostatic interaction at the amino termini of the oligourea by leaving the Boc protective groups on. The CD spectra of both Boc-protected and the corresponding deprotected homochiral and heterochiral heterostructural triureas based on DACH and DPEDA were taken in MeOH (**Figure 3.14**). From the CD curves, one can tell that capping the end with Boc doesn't change the global conformation, but it does have some effect on the concentration of different global conformations.

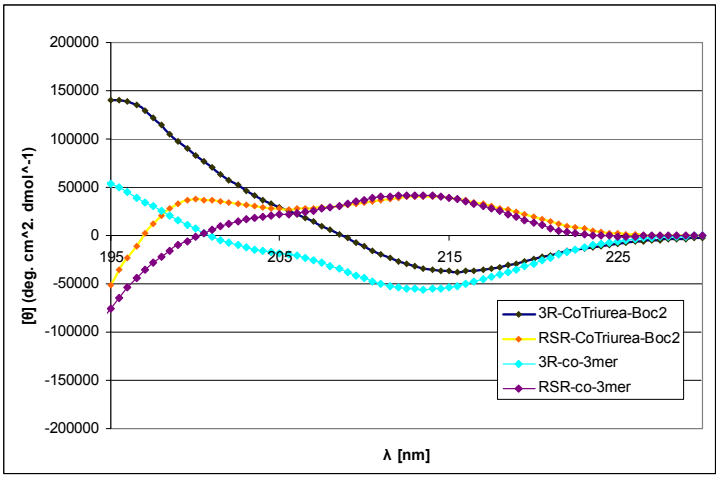


Figure 3.14 Capping effect studied by CD

The study of capping effect for other oligoureas was inhibited by the poor solubility of the Boc protected compounds.

3.3.2.2 Conformational study of homochiral oligoureas

As mentioned before, the exact solution state conformation can not be determined by just looking at the CD curves, but combined with crystal structure and NMR study, much conformational information about these oligoureas can be inferred. This will be shown in the following sections.

3.3.2.2.1 Homochiral oligoureas based on DACH-conformation and cooperativity

The CD spectra of all R $(DACH)_n$ series were taken in both water and MeOH. **Figures 3.15 and 3.16** show far-UV CD data for homologous series of *trans*-1,2-DACH in water and methanol solution. The data have been normalized for both oligourea concentration and the number of urea chromophores in each molecule. The vertical axis represents molar ellipticity per residue. The CD signal varies significantly across the series. In water, the study is limited to oligoureas with chain lengths from 3 to 6 because of the poor solubility of the longer oligoureas, while in MeOH, even an octaurea can be successfully examined.

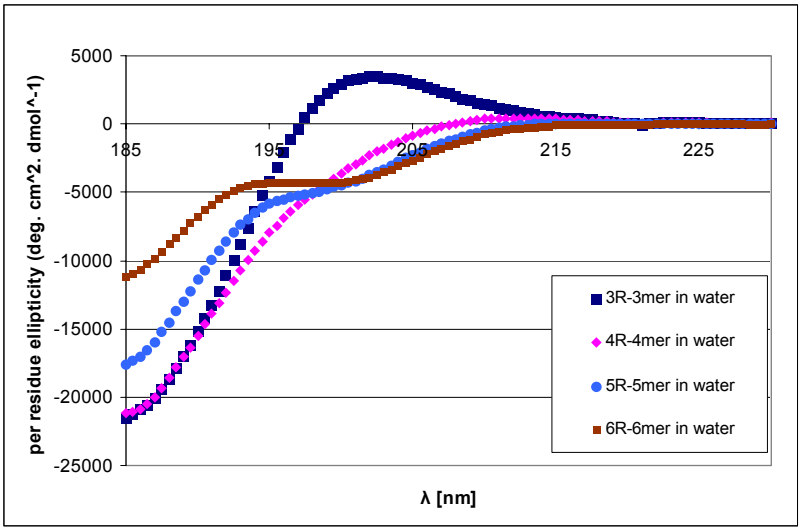


Figure 3.15 CD spectra of homochiral DACH oligoureas in water

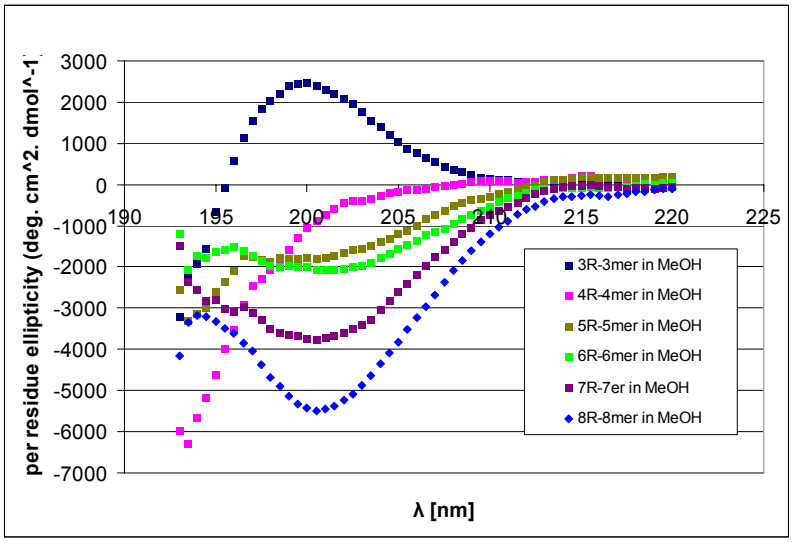


Figure 3.16 CD spectra of homochiral DACH oligoureas in MeOH

In both water and MeOH, the triurea shows a maximum at around 200 nm, while the tetraurea shows no maximum or minimum, but from pentaurea on, the oligoureas show a minimum. The difference is in MeOH, the trough is more obvious for each compound. And as the chain becomes longer, the molar elliplicity becomes larger (absolute value). For peptides, it is known that their helical preference increases upon moving them from H_2O to alcoholic solvents.[19-25] Here the same conformation effect of MeOH might be true for these oligoureas.

From the CD curves, it can be inferred that there is a global conformation change as the chain elongates. Although the exact conformation can not be said from the CD curves, combined with the X-ray structure of the homochiral triurea (an extended structure) and the X-ray structure of the heterochiral oligourea (a helix like structure) and its CD (which has a minimum), plus the

known helix stabilizing effect of MeOH, probably one can postulate the global conformation changed from mainly extended to mainly helix, and tetrauea is the turning point.

Further examining the contribution to the CD signal from a single residue of each oligourea in MeOH, the cooperative behavior can be observed. From the CD curves, it is known that from pentaurea on, these oligoureas have a similar conformation (probably helix), and as the chain length increases, the contribution to the conformation of each residue becomes larger, that means the concentration of helices increases with the addition of another residue. If no cooperativity exists, the mean residue molar ellipticity should stay the same.

3.3.2.2.2 Homochiral oligoureas based on DACH and DPEDA-conformation

A circular dichroism study was also carried out for homochiral heterostructural oligoureas. Although definitive conclusions can not be drawn at this stage, a lot of preliminary deductions can be made.

For the heterostructural oligoureas based on DACH and DPEDA, the CD curves for triurea, pentaurea and heptaurea are similar. All show a minimum and a maximum, but for the pentaurea and heptaurea, both the minimum and maximum red-shifted a few nanometers. Considering the fact that the solid state conformation of both triurea and pentaurea is extended, and the ROESY NMR for both pentaurea and heptaurea doesn't show long range NOEs, the dominant solution conformation for them might be extended.

The CD spectra are shown in **Figure 3.17.**

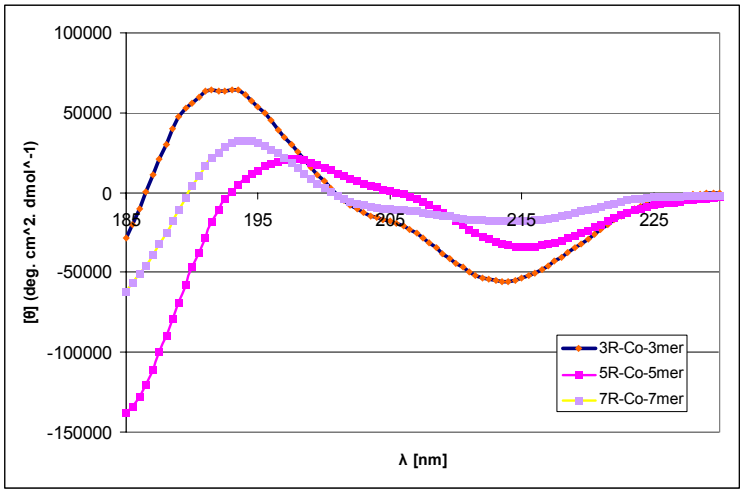


Figure 3.17 CD spectra of homochiral oligoureas based on DACH and DPEDA

3.3.2.2.3 Homochiral oligoureas based on different monomers

Other oligoureas were made to study the effect of local monomers. The following figure shows the effect of the incorporation of an achiral residue 1,2-ethylenediamine. The triurea

shows a distinct CD curve, which is different from the corresponding DACH triurea. Considering the C-C rotation of the achiral unit has a low energy barrier compared with the relatively rigid cyclohexane ring, the conformation of the EDA triurea probably is at random state. With the addition of two other DACH residues, the conformation is made to be similar to DACH triurea. Although the rotation still exists, the preference for extended structure of the two end DACH diureas could force the whole molecule to form an extended structure (but this seems to be contradictory to the prediction made by the molecular modeling). The spectra are shown in **Figure 3.18.**

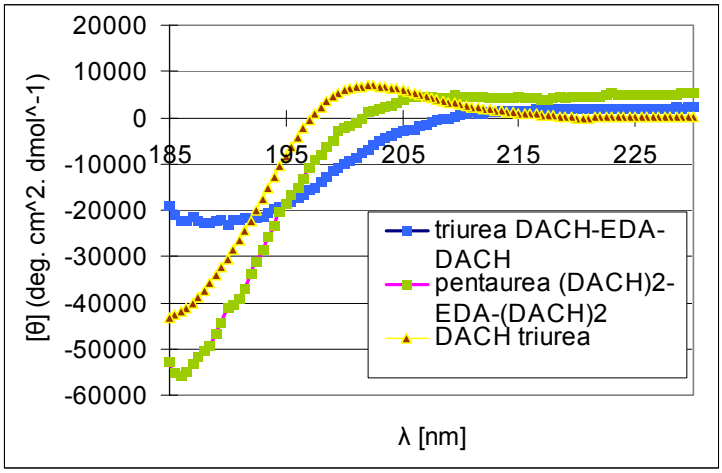


Figure 3.18 CD spectra of oligoureas based on both EDA and DACH in H_2O

Also, oligoureas with three different diamines were synthesized. One example is given below (**Figure 3.19**). For the pentaurea DPEDA-DACH-NBDAP-DACH-DPEDA, both the Boc protected form and the deprotected form have the same conformation in MeOH, which in general is similar to the heterostructural pentaurea $(DACH)_2$-DPEDA-$(DACH)_2$.

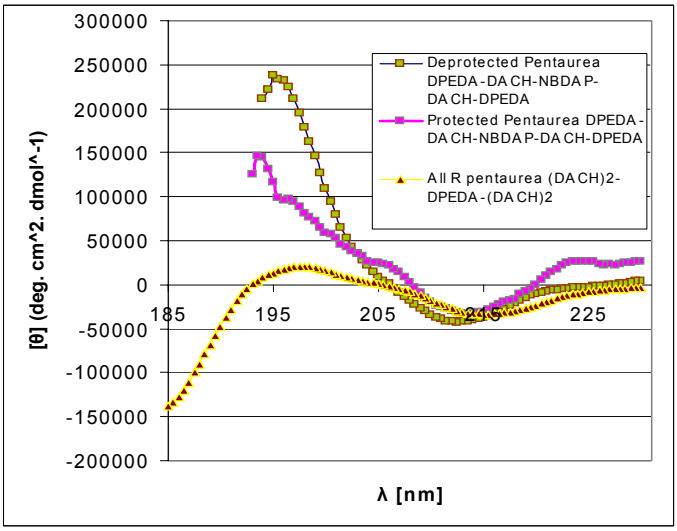


Figure 3.19 CD Spectra of oligourea DPEDA-DACH-NBDAP-DACH-DPEDA

3.3.2.3 Conformational study of heterochiral oligoureas

Circular dichroism was also applied to study the conformation of the heterochiral oligoureas.

3.3.2.3.1 Alternate RS oligoureas based on DACH-conformation and cooperativity

The oligoureas with alternate RS DACH residues take the same conformation in water according to the CD curves (these oligoureas are designed to have an odd number of residues because they are chiral while alternate RS oligoureas with an even number of residues are achiral, for example: RSRSRS). Heterochiral triurea is known to form a helix in the solid state from its crystal structure. If the same conformation is taken in solution (which could be because the helical preference is intrinsic), then all these oligoureas have the helix conformation in solution (**Figure 3.20**).

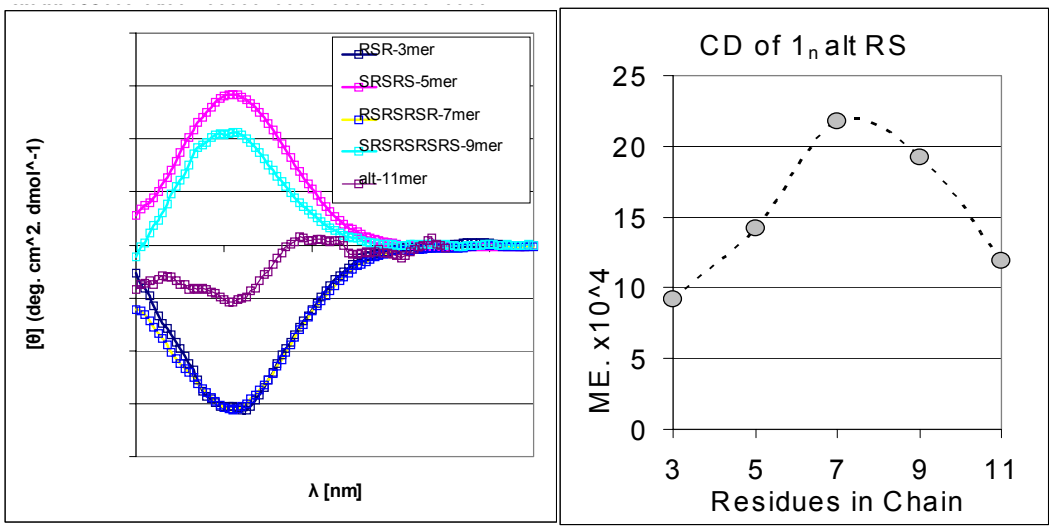


Figure 3.20 CD spectra of alternate RS DACH oligoureas and the cooperative behavior

As the chain length increases, the ee% of the chains decreases because ee% = [R - S]/[R + S] = 1/[R +S]. For example, for RSR-triurea, ee% = 1/3 = 33.3%, and for undecaurea, ee% = 1/11 = 9.1%.

If no cooperative behavior exists for these alternate RS oligoureas, then the absolute value of molar elliplicity should decrease as the chain elongates, but instead of decrease, the molar elliplicity increases from triurea to heptaurea, then it decreases from heptaurea to undecaurea.

3.3.2.3.2 Heterochiral DACH oligoureas (S monomer in the middle)-conformation

The conformation of two other heterochiral oligoureas based on DACH was also studied by CD. These two oligoureas have (S,S)-DACH in the middle of a chain of (R,R)-DACHs. The

conformation is compared with the all R DACH triurea and RSR-DACH triurea. For the pentaurea and heptaurea, their conformation is totally different from that of RSR-DACH triurea, and similar to all R DACH triurea. The insertion of an (S,S) monomer breaks the continuation of the homochiral chain, introducing helicity in the central three residues, but there is a competition from the end homochiral residues, and there is also a competition from the whole chain. For the pentaurea, the conformational preference of the two ends dominates, which happens to be extended structure, but for the heptaurea, although the two ends still prefer extended structure, as the chain elongates, the whole molecule tends to form a helix just as the homochiral heptaurea does, and the middle (S,S) residue plays a role here, so the global conformation is more like that of the homochiral tetraurea, which happens to be the turning point from extended structure to helix. One should not be surprised if the nonaurea with (S,S) monomer in the middle and longer ones take the helix conformation again (**Figure 3.21**).

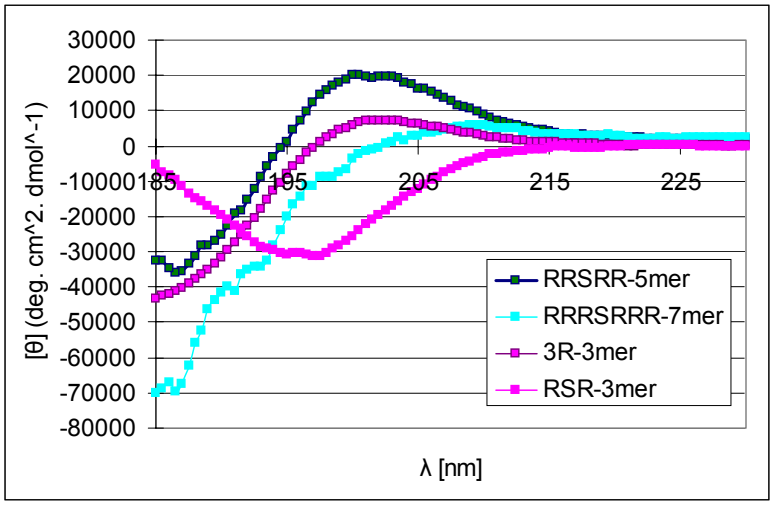


Figure 3.21 CD spectra of heterochiral DACH oligoureas

3.3.2.3.3 Heterochiral oligoureas based on DACH and DPEDA

The conformations of the heterochiral oligoureas based on both DACH and DPEDA are similar in solution. Considering the solid conformation of RSR DACH-DPEDA-DACH triurea is a helix, as shown by its crystal structure, the solution conformation of these oligureas could be helical. At the same time, it is obvious the conformations of these heterochiral oligoureas are different from that of the homochiral pentaurea $(DACH)_2$-DPEDA-$(DACH)_2$ (**Figure 3.22**).

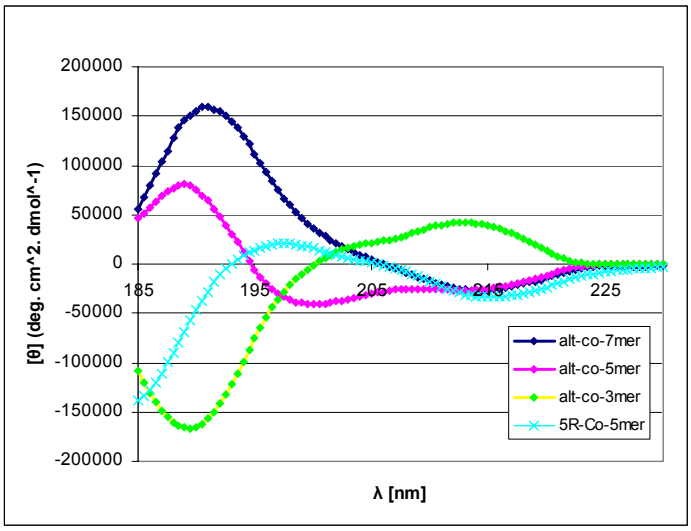


Figure 3.22 CD spectra of alternate RS oligoureas based on DACH and DPEDA

3.3.2.3.4 Heterochiral oligoureas based on DACH and DPEDA (S DPEDA in the middle)

While there is a conformation change for oligoureas based on only DACH with heterochiral residue in the middle as the chain becomes longer, for the heterostructural ones with (S,S) DPEDA in the middle but the main chain is based on DACH, the conformation is consistent, which means the local residue does control the conformation of the whole molecule just as EDA did (**Figure 3.23**).

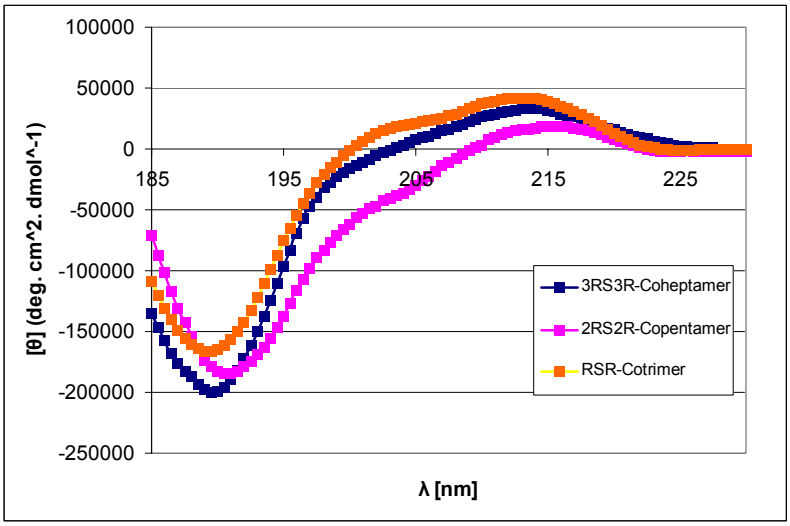


Figure 3.23 CD spectra of heterochiral oligoureas based on DACH and DPEDA

3.3.2.4 The effect of solvent on the conformation

Biomolecules are known to be sensitive to solvents. One interesting factor about these oligoureas is the solvent sensitivity of some of the oligoureas.

For example, the CD spectra for both homochiral and heterochiral triueas based on DACH were taken in H_2O and CH_3CN. For the homochiral triurea, the CD in water shows a maximum,

while the same compound in CH_3CN gives a minimum. In contrast, the CD spectra for heterochiral triurea in both water and CH_3CN are similar; only the intensity is different. The homochiral triurea is known from the crystal structure to form an extended structure, while the heterochiral triurea forms a helix-like structure. That means in less competitive solvents (less polar), the homochiral triurea changes its conformation from extended structure to helix, while for the heterochiral triurea, which has an intrinsic helix conformation, the solvent CH_3CN doesn't have too much effect. A possible explanation is shown in **Figure 3.24.**

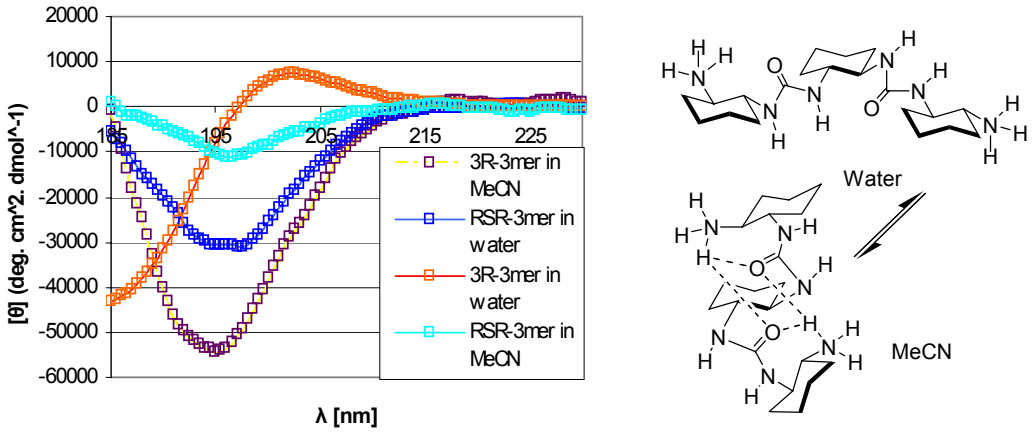


Figure 3.24 CD spectra of both homochiral and heterochiral DACH triureas in H_2O and CH_3CN

The same conformation change is observed for DACH tetraurea (**Figure 3.25**). Although the solubility of the tetraurea limits the quantitative study, the CD curve shows a minimum for tetraurea in CH_3CN compared with no maximum or minimum for it in water.

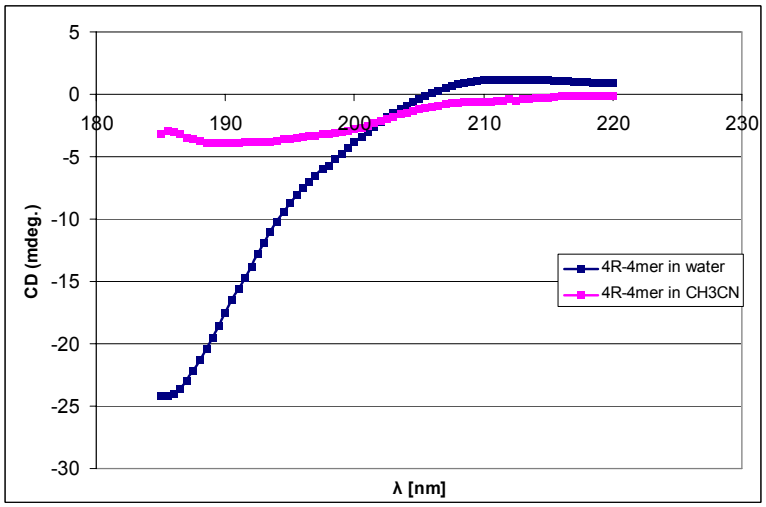


Figure 3.25 CD spectra of all R DACH tetraurea in water and CH_3CN

The solvent-sensitive behavior of oligoureas actually provides further evidence that these spectral signatures are associated with global conformation. What's stunning is that the solvent doesn't play the same role for the heterostructural oligoureas based on both DACH and DPEDA.

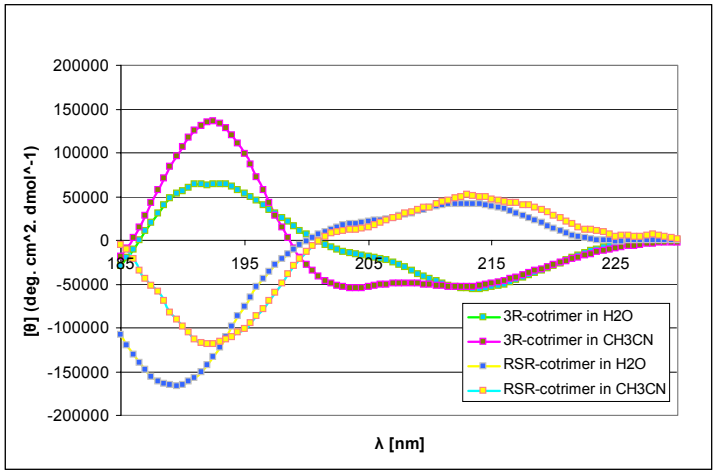


Figure 3.26 CD spectra of homochiral and heterochiral oligoureas based on DACH and DPEDA in water and CH_3CN

As shown in **Figure 3.26**, the conformation of the homochiral triurea DACH-DPEDA-DACH in both water and CH_3CN is generally similar except for the difference in intensity. For the heterochiral cotriurea, the same observation was made, but the CD curve in CH_3CN shows a red shift, and the intensity is lowered, which is similar to what CH_3CN did for the RSR DACH triurea (no conformation change, but the intensity decreases). What this implies is that the side chains do have an effect on the stability of the conformations of these oligoureas. Here, π-stacking probably stabilizes the conformation.

The same behavior is observed for longer heterochiral oligoureas based on DACH and DPEDA. For the alternate heterostructural oligourea, the red shift of the CD curve still exists (**Figure 3.27**).

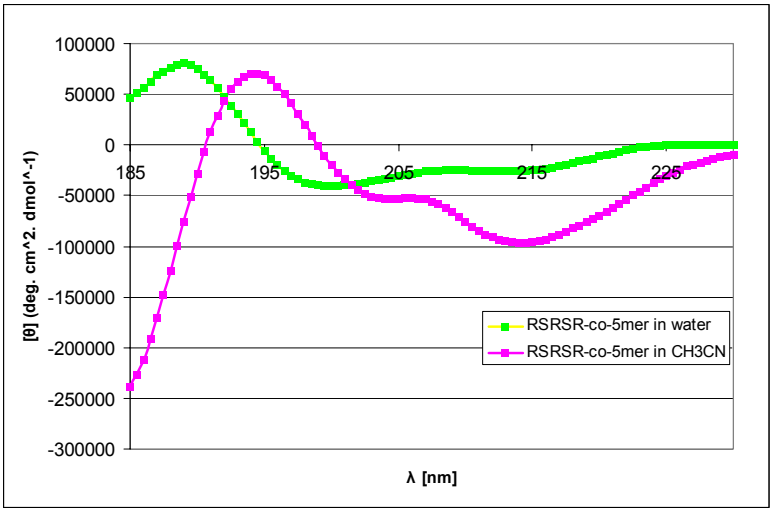


Figure 3.27 CD spectra of alternate RS oligoureas $DACH_2$-DPEDA-$DACH_2$

And even for the other kinds of heterostructural and heterochiral oligureas, the same observation is made (**Figure 3.28**).

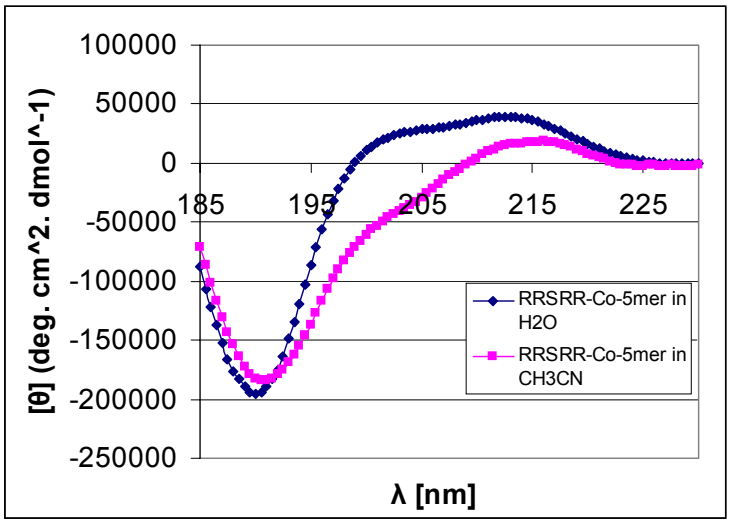


Figure 3.28 CD Spectra of RRSRR pentaurea $(DACH)_2$-DPEDA-$(DACH)_2$ in H_2O and CH_3CN

The effect of other solvents on the conformation was also investigated. These include MeOH, trifluoroethanol (TFE), and hexafluoroisopropanol (HFIP). Addition of certain alcohols such as MeOH, TFE and HFIP to water at a low concentration is known to enhance the helicity of medium-sized peptides with an intrinsic tendency to assume helical conformation in water.[26-29] This effect is also observed in these chiral oligoureas. In general, the conformation of these oligoureas is similar in both MeOH and water, except that in MeOH, the helix is stabilized, which was shown before as well as in the following example (**Figure 3.29**). For the homochiral triurea based on DACH, the CD spectra in water, MeOH and 15% TFE are similar, no conformation change is observed.

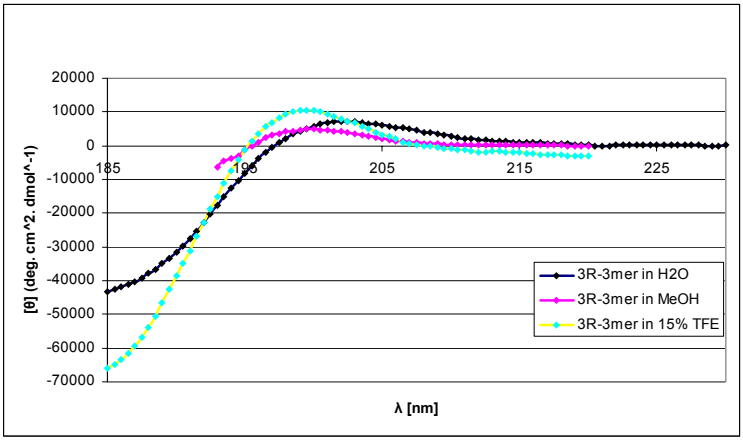


Figure 3.29 CD spectra of homochiral DACH triurea in H_2O, MeOH and 15% TFE.

But in TFE and HFIP, the conformational change is obvious for longer homochiral oligoureas such as DACH hexaurea and heptaurea. TFE and HFIP are known to enhance the helicity of peptides with intrinsic helical conformation preference. It is shown from the CD spectra in water, 15% TFE and 50% HFIP for both hexaurea and heptaurea based on DACH that the helical conformation is stabilized in both TFE and HFIP (**Figures 3.30, 3.31,** and **3.32**). Compared with TFE, HFIP shows stronger helicity enhancement ability.

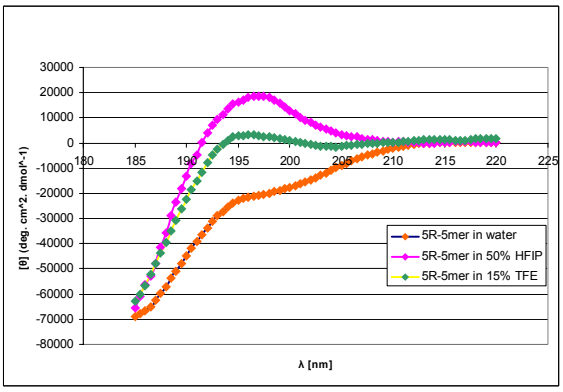


Figure 3.30 CD spectra of all R DACH hexaurea in water, 15% TFE and 50% HFIP

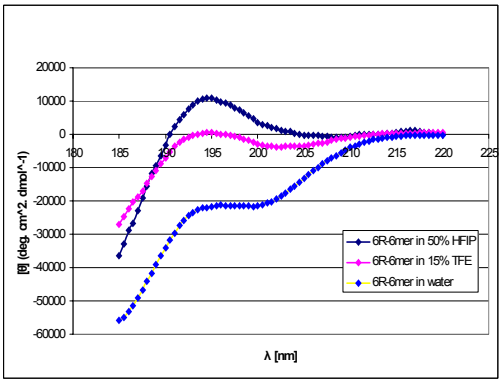


Figure 3.31 CD spectra of all R DACH heptaurea in water 15% TFE and 50% HFIP

Further comparison of the CD spectra of pentaurea, hexaurea and heptaurea in 15% TFE with the CD spectrum of homochiral triurea in water makes the conformation difference obvious.

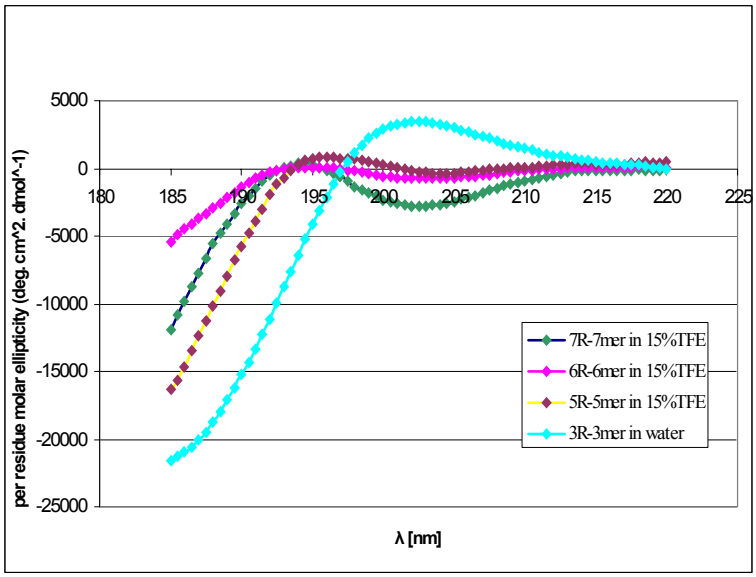


Figure 3.32 CD spectra of homochiral DACH pentaurea, hexaurea and heptaurea in 15% TFE and homochiral DACH triurea in water

3.3.2.5 The effect of temperature on the conformation

Proteins are known to denature at higher temperatures, and DNA also "melts" at elevated temperatures, but for unnatural oligomers, such behavior is not well-documented.[30] One other intriguing aspect of these oligoureas is the effect of temperature on the conformation. The general trend for the thermal stability of the conformations is: for oligoureas that tend to assume an extended structure, conformation is not perturbed greatly with temperature, but for those with a conformational preference for the putative helix, the conformation "melts" with increased temperature. For homochiral oligoureas based on DACH, this trend is more obvious than the corresponding heterochiral series.

For all R triurea DACH-DPEDA-DACH, the conformation in water at 10°C is the same as the conformation at 50°C, and the same observation is made for all R triurea, tetraurea and pentaurea based on DACH. But for hexaurea and other longer oligoureas, the conformation changes as the temperature increases.

Figure 3.33 shows the CD spectra of all R triurea DACH-DPEDA-DACH at 10 °C and 50 °C. No conformation change is observed, and the conformation is stable for this oligourea.

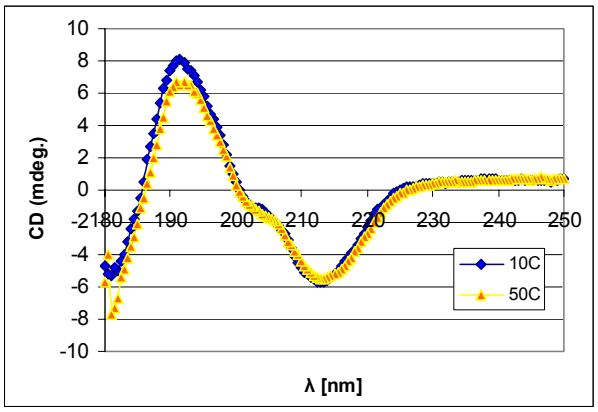


Figure 3.33 CD spectra of homochiral triurea based on DACH and DPEDA at different temperatures

For all R tetraurea and pentaurea based on DACH, the CD spectra are identical at 20 °C and 50 °C for both compounds, as shown in **Figure 3.34.**

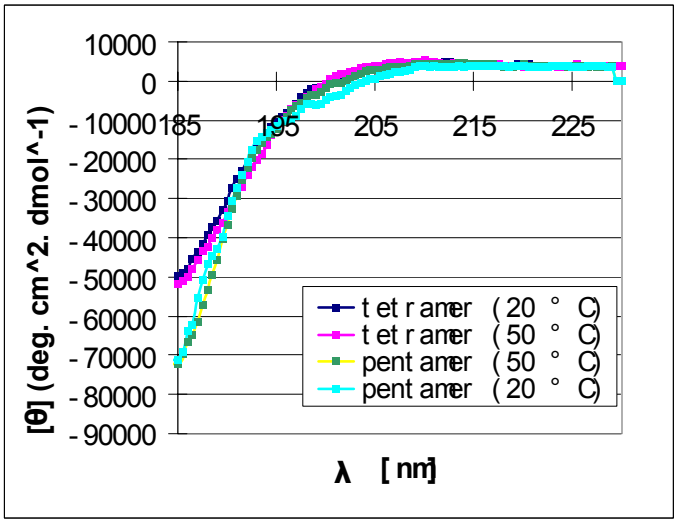


Figure 3.34 CD spectra of homochiral DACH tetraurea and pentaurea at different temperatures.
(The solvent is 2% HFIP.)

For all R DACH hexaurea, the conformation experiences a change when the temperature is increased from 5°C to 95°C, but as the temperature returns back to 5°C, the conformation recovers again (**Figure 3.35**).

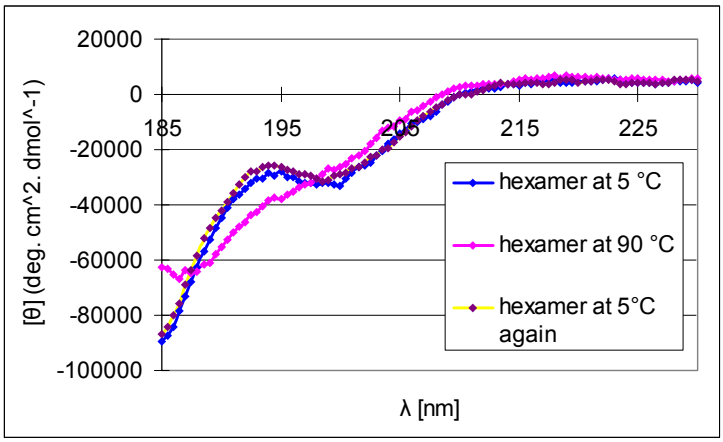


Figure 3.35 CD spectra of homochiral DACH hexaurea at different temperatures

This "melting" behavior is even more obvious for the all R DACH nonaurea in 15% TFE (**Figure 3.36**). In contrast, the conformation of the corresponding alternate RS oligoureas is relatively stable although it changes with the temperature variation too (**Figure 3.37**).

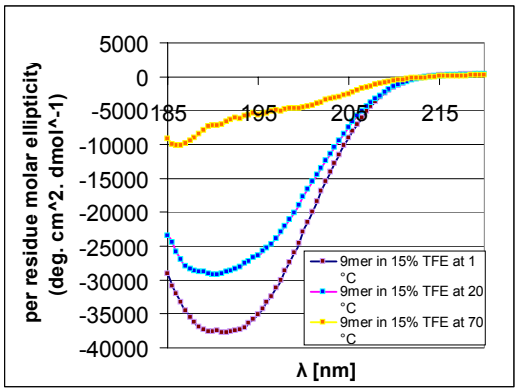


Figure 3.36 CD spectra of all R DACH nonaurea at different temperatures

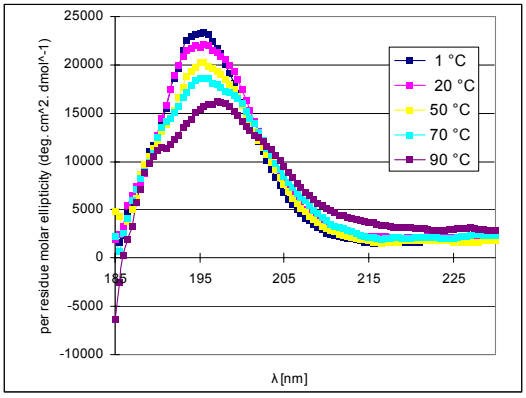


Figure 3.37 CD spectra of alternate RS DACH nonaurea at different temperatures

The conformation of the alternate RS oligoureas based on DACH and DPEDA is also relatively stable as shown in **Figure 3.38**.

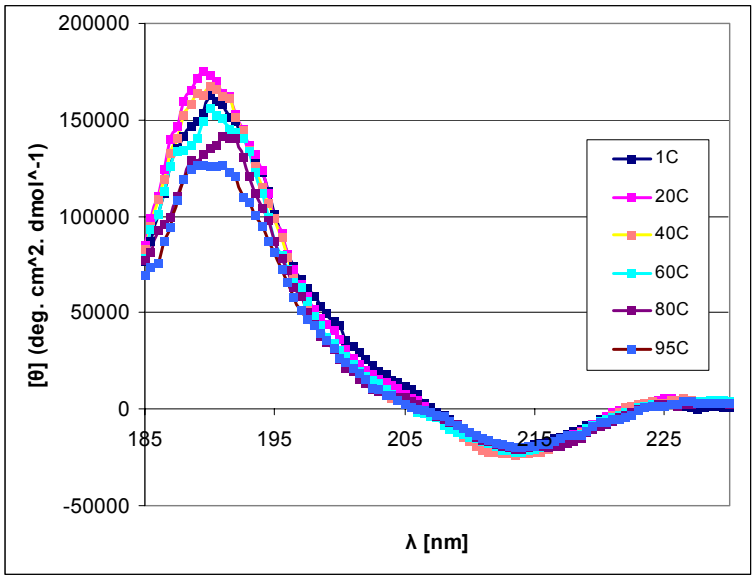


Figure 3.38 CD spectra of alternate RS heptaurea based on both DACH and DPEDA at different temperatures

3.4 Solubility study of homochiral and alternate RS DACH oligoureas

To gather further evidence for the helix preference of alternate chiral oligoureas, the solubility in water of both the all R and alternate RS DACH heptaureas was studied by UV-Vis. The solubility of the alternate RS oligourea is shown to be 1.7 mg/mL, while the homochiral one has aqueous solubility less than 0.01 mg/mL. If the alternate RS oligoureas prefer helix over extended structure in general, then the solubility should be understandably higher, because the extended oligoureas could aggregate in water to decrease the solubility.

3.5 Conclusions

A conformational study of chiral oligoureas was done in both solid state and solution state. The crystal structures of some homochiral oligoureas and some alternate RS oligoureas indicate that both helix-like structures and extended structures exist for these C_2-symmetric oligoureas. So far, the conformational study by NMR is not conclusive. CD studies show that these oligoureas have multiple conformations in solution, and some of the conformations are sensitive to solvents and temperature. Also, both homochiral and alternate chiral oligoureas based on DACH exhibit cooperative behavior in solution.

3.6 Future work

The utmost purpose of this work is to design biomimetic molecules. To achieve that goal, conformation specificity is required, i.e. the target molecules should have a stable and specific 3-D structure (for example, helix) in solution. The preliminary results of this work indicate that homochiral and homogeneous oligoureas with longer chain length tend to form helical structure

in solution, but the solubility might dampen its application; introduction of enantiomeric units into these chain molecules (for example, the preparation of chain molecule of alternate chiral monomers) induces helicity to the oligomers, and the solubility of the resultant molecule can also be improved. This information should provide valuable guidance for future study in this field.

3.7 References

(1) Gellman, S. H. *Acc. Chem. Res*. **1998**, *31*, 173.

(2) Giacovazzo, C. *Fundamentals of Crystallography;* Oxford University Press: Oxford, 2002.

(3) Englander, S. W.; Kanllenbach, N. R. Q. *Rev. Biophys*. **1984**, *16*, 521.

(4) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc*. **1996**, *118*, 13071.

(5) Stevens, E. S.; Sugawara, N.; Bonara, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7048.

(6) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512.

(7) Holzwarth, G. M.; Doty, P. *J. Am. Chem. Soc.* **1965**, *87*, 218.

(8) Engle, A. R.; Purdie, N.; Hyatt, J. A. *Carbohydr. Res.* **1994**, *265*, 181.

(9) Wiesler, W. T.; Berova, N.; Ojika, M.; Meyers, H. V.; Chang, M.; Zhou, P.; Lo, L.-C.; Niwa, M.; Takeda, R.; Nakanishi, K. *Helv. Chim. Acta* **1990**, *73*, 509.

(10) Perczel, A.; Kollat, E.; Hollosi, M.; Fasman, G. D. *Biopolymers* **1993**, *33*, 665.

(11) Melton, L. D.; Morris, E. R.; Rees, D. A.; Thom, D. *J. Chem. Soc., Perkin Trans. 2* **1979**, 10.

(12) Listowsky, I.; Avigad, G.; Englard, S. *J. Org. Chem.* **1970**, *35*, 1080.

(13) Comb, D. G.; Roseman, S. *J. Biol. Chem.* **1960**, *235*, 2529.

(14) Dewitt, C. W.; Zell, E. A. *J. Bacteriol.* **1961**, *82*, 849.

(15) Blacklow, R. S.; Warren, L. *J. Biol. Chem.* **1962**, *237*, 3520.

(16) McReynolds, K. D.; Gervay-Hague, J. *Tetrahedron: Asym.* **2000***, 11,* 337.

(17) Berova, N.; Nakanishi, K.; Woody, R. W. Circular Dichroism: Principles and Applications; 2nd Edition, Wiley-VCH, 2000.

(18) Rodger, A.; Norden, B. Circular dichroism and linear dichroism; Oxford University Press, 1997.

(19) Epand, R. M.; Scheraga, H. A. *Biopolymers* **1968**, *6*, 1551.

(20) Yaron, A.; Katchalski, E.; Berger, A.; Fasman, G. D.; Bover, H. A. *Biopolymers* **1971**, *10*, 1107.

(21) Conio, G.; Patrone, E. *Biopolymers* **1969**, *8*, 57.

(22) Conio, G.; Patrone, E.; Brighetti, S. *J. Biol. Chem.* **1970**, *245*, 3335.

(23) Satoh, M.; Fujii, Y.; Kato, F.; Komiyama, J. *Biopolymers* **1991**, *31*, 1.

(24) Bianchi, E.; Rampone, R.; Tealdi, A.; Ciferri, A. *J. Biol. Chem.* **1970**, *245*, 3341.

(25) Bello, J. *Biopolymers* **1993**, *33*, 491.

(26) Goodman, M.; Listowsky, L.; Masuda, Y.; Boardman, F. *Biopolymers* **1963**, *1*, 33.

(27) Goodman, M.; Rosen, I. G. *Biopolymers* **1964**, *2*, 537.

(28) Goodman, M.; Verdini, A. S.; Toniolo, C.; Phillips, W. D.; Bovey, F. A. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *64*, 444.

(29) Cammers, A.; Allen, T. J.; Oslick, S. L.; McClure, K. F.; Lee, J. H.; Kemp, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 3082.

(30) Zubay, G. L. *Biochemistry* 4th ed, Wm. C. Brown Publisher, 1998.

Chapter 4 Synthesis and Experiments

4.1 Preparation of monomers

Five C_2-symmetric 1,2-diamines were used as the building blocks for the oligoureas. Among them, 1,2-diaminoethane, (*R,R*)-1,2-diaminocyclohexane mono-(+)-tartaric acid salt and (*S,S*)-1,2-diaminocyclohexane mono-(-)-tartaric acid salt, (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (DPEDA) and its enantiomer are commercially available. But because of expense, both enantiomers of 1,2-diaminocyclohexane (DACH) were obtained through resolution followed by base neutralization (**Figure 4.1**),[1] and both enantiomers of diphenylethylenediamine were prepared by synthesis followed by resolution and neutralization (**Figure 4.2**).[2] 3,4-Diamino-1-benzylpyrrolidines and (*R*,*R*)-3,4-diaminotetrahydrofuran were also synthesized through a series of reactions (**Figure 4.3**).[3]

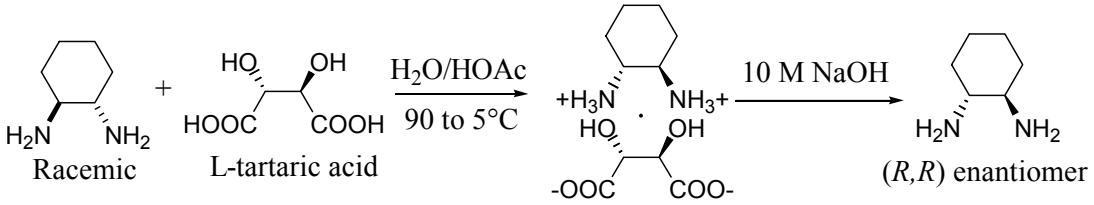


Figure 4.1 Resolution of racemic 1,2-diaminocyclohexane

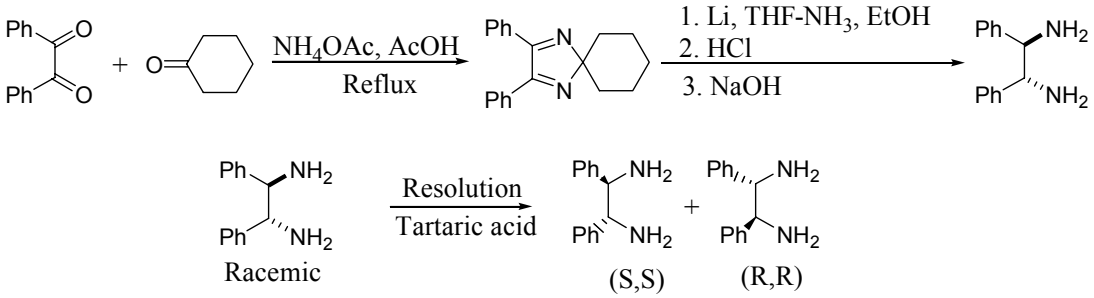


Figure 4.2 Synthesis and resolution of racemic1,2-diphenylethylenediamines

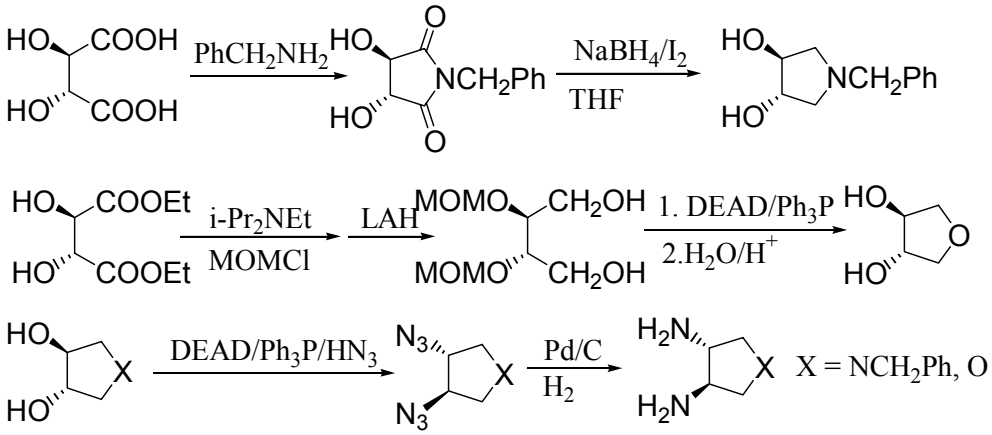


Figure 4.3 Synthesis of 3,4-diamino-1-benzylpyrrolidines and (R,R)-3,4-diaminotetrahydrofuran

4.2 Synthesis of oligoureas

The synthetic challenge lies in the fact that an efficient way to approach the target molecules needs to be found. Both solid phase synthesis (SPS) and solution phase synthesis have been considered for the synthesis of the oligomers. Due to the nature of the target molecules, solid phase synthesis might be the best choice because of its advantages in sequence control, ease of purification and speed, but solution phase synthesis might provide the necessary guidance for SPS. All the syntheses were carried out in solution phase.

4.2.1 Synthesis of homo- and heterochiral DACH oligoureas

The synthetic process is shown in **Figure 4.4**. Optically pure (1*R*, 2*R*)-*trans*-1, 2-diaminocyclohexane **1** was monoprotected with *tert*-butoxycarbonyl (Boc) and trifluoroacetyl (Tfa) to give **2** and **3** respectively. Boc and Tfa were chosen because they are orthogonal to each other.[4,5] Intermediate **4** was prepared by the activation of compound **3** with *para*-nitrophenyl chloroformate (PNP)**.**[6] Dimerization of **2/3** and **4** gave Boc-protected and differentially protected diureas **5, 6.** (X-ray structures of **5**, **6** were obtained.) Compounds **7** and **8** were obtained by removing one of the two orthogonal protecting groups in a facile manner.[7]

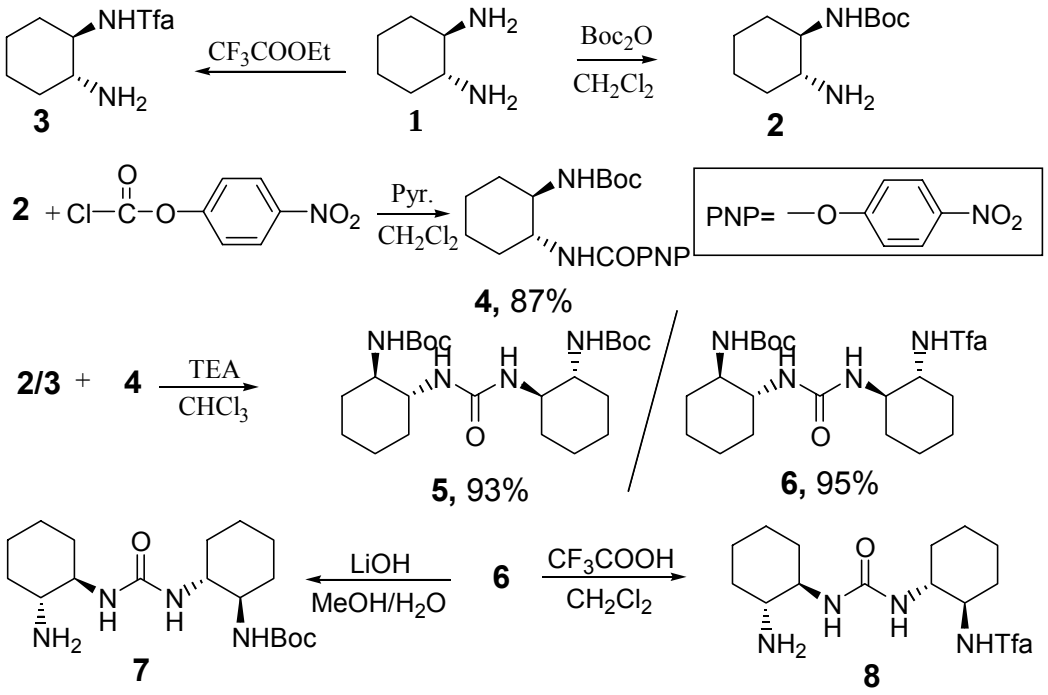


Figure 4.4 Synthesis of DACH diureas

Theoretically, both stepwise addition and fragment condensation could be used to further elongate the chain length. Stepwise addition involves growing an oligomer by adding one monomer or two monomers at a time to a "free" terminus or two termini. This method is used to prepare smaller products, aperiodic sequences, and short oligomers for fragment condensation.[8] Fragment condensation is a synthetic method which involves coupling two or more oligomer moieties to longer and heavier molecular components.[9] Both stepwise addition and fragment condensation have been tested.

Differentially protected triurea **9** and tetraurea **11** were synthesized by adding one unit a time with compound **4** as the intermediate (**Figure 4.5**).

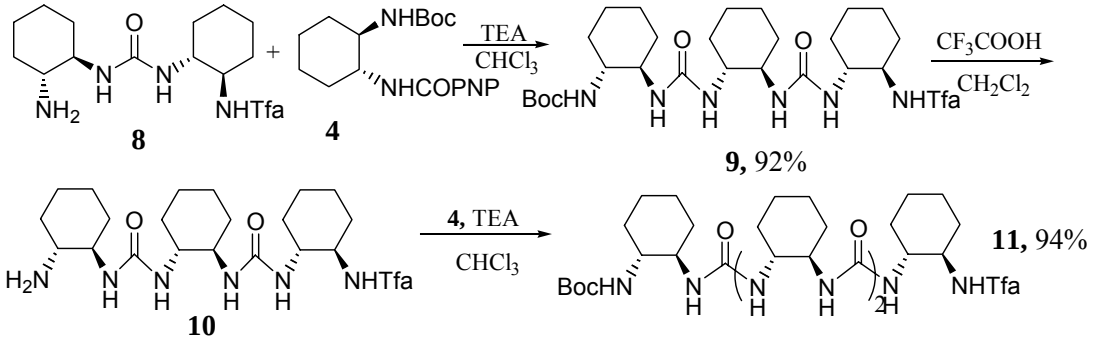
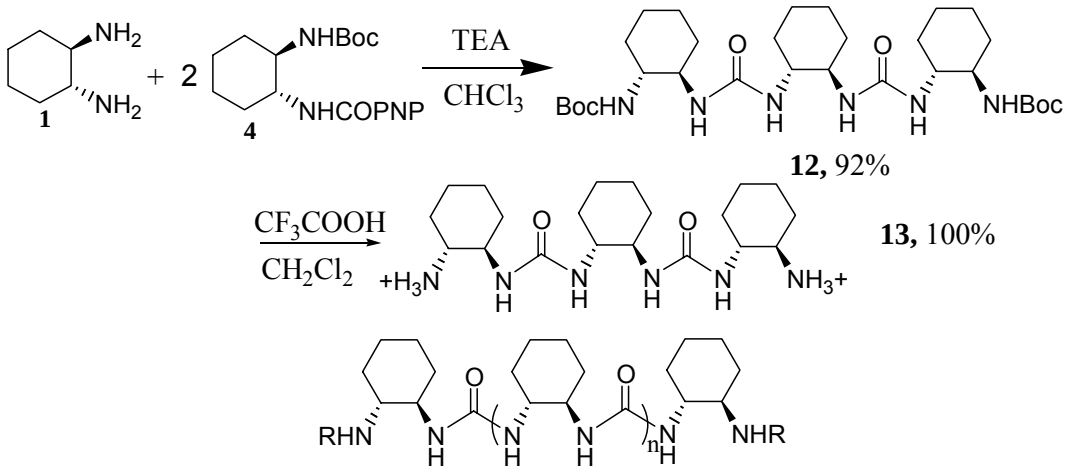


Figure 4.5 Synthesis of differentially protected DACH triurea and tetraurea

Boc protected triurea **12** was prepared by mixing diamine **1** with two equivalents of intermediate **4**. Removing Boc with CF_3COOH followed by addition of two equivalents of **4** led to an oligourea with two more units. Both Boc-protected and Boc-removed tetraurea **15** and **16**, pentaurea **17** and **18**, hexaurea **19** and **20**, heptaurea **21** and **22,** octaurea **23** and **24,** nonaurea **25** and **26** were prepared by the same method (**Figure 4.6**).



n = 0: R = H (**14**), 100%; n = 2: R = tBoc (**15**), 91%, R = H (**16**);
n = 3: R = tBoc (**17**), 87%, R = H (**18**); n = 4: R = tBoc (**19**), 87%, R = H (**20**);
n = 5: R = tBoc (**21**), 80%, R = H (**22**); n = 6: R = tBoc (**23**), 77%, R = H (**24**);
n = 7: R = tBoc (**25**), 70%, R = H (**26**).

Figure 4.6 Further elongation of the chain

The alternate RS DACH oligoureas **27** to **31** were made by the same method (**Figure 4.7**).

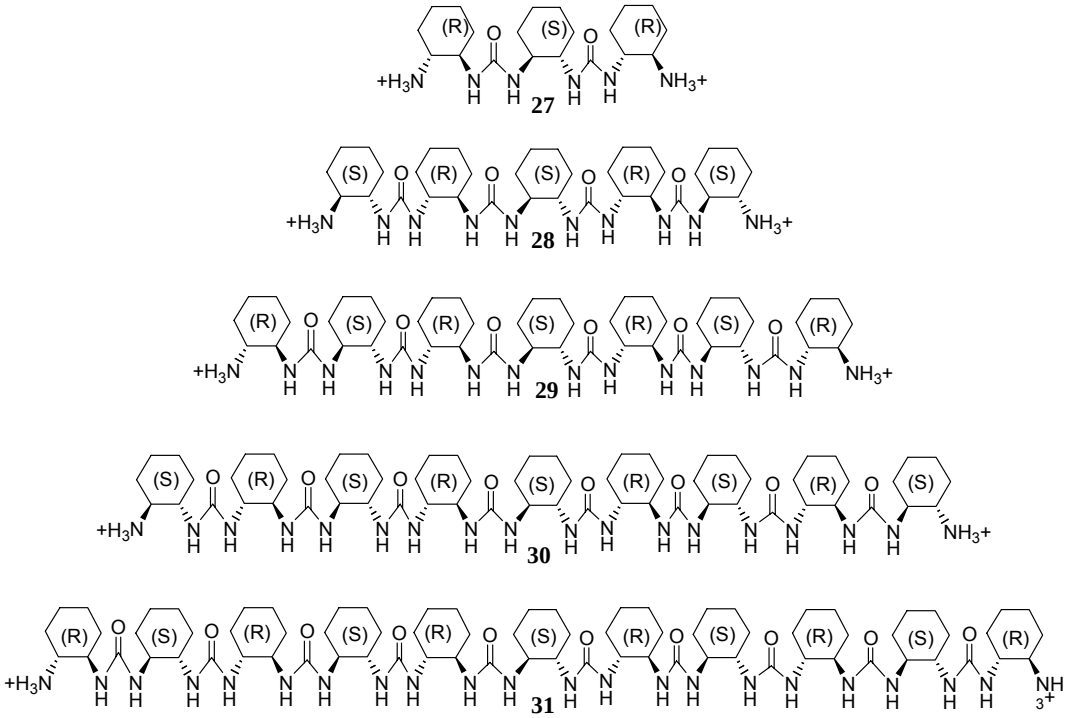


Figure 4.7 Alternate RS DACH oligoureas

Also an RRSRR DACH pentaurea and an RRRSRRR DACH heptaurea were prepared (**Figure 4.8**).

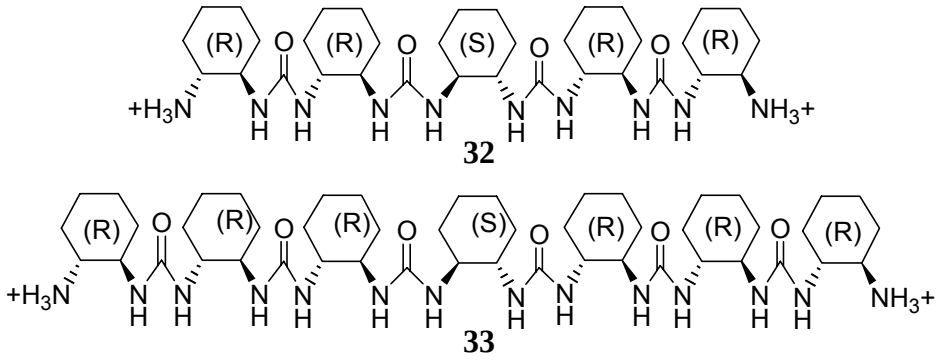


Figure 4.8 Two other heterochiral DACH oligoureas

4.2.2 Synthesis of homo- and heterochiral oligoureas based on diverse monomers

Heterostructural oligoureas with both (1*R*, 2*R*)-*trans*-1, 2-diaminocyclohexane and (1*R*, 2*R*)-1, 2-diphenylethylenediamine as building blocks were made first by the same method (**Figure 4.9**).

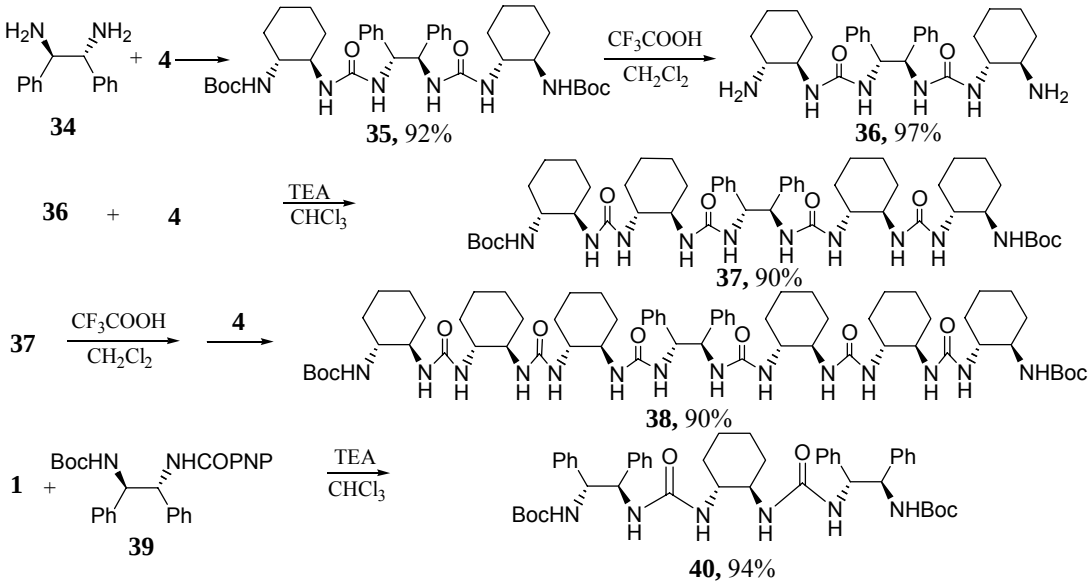


Figure 4.9 Synthesis of all R heterostructural oligoureas

Then heterochiral oligoureas based on DACH and DPEDA were synthesized too (**Figure 4.10**).

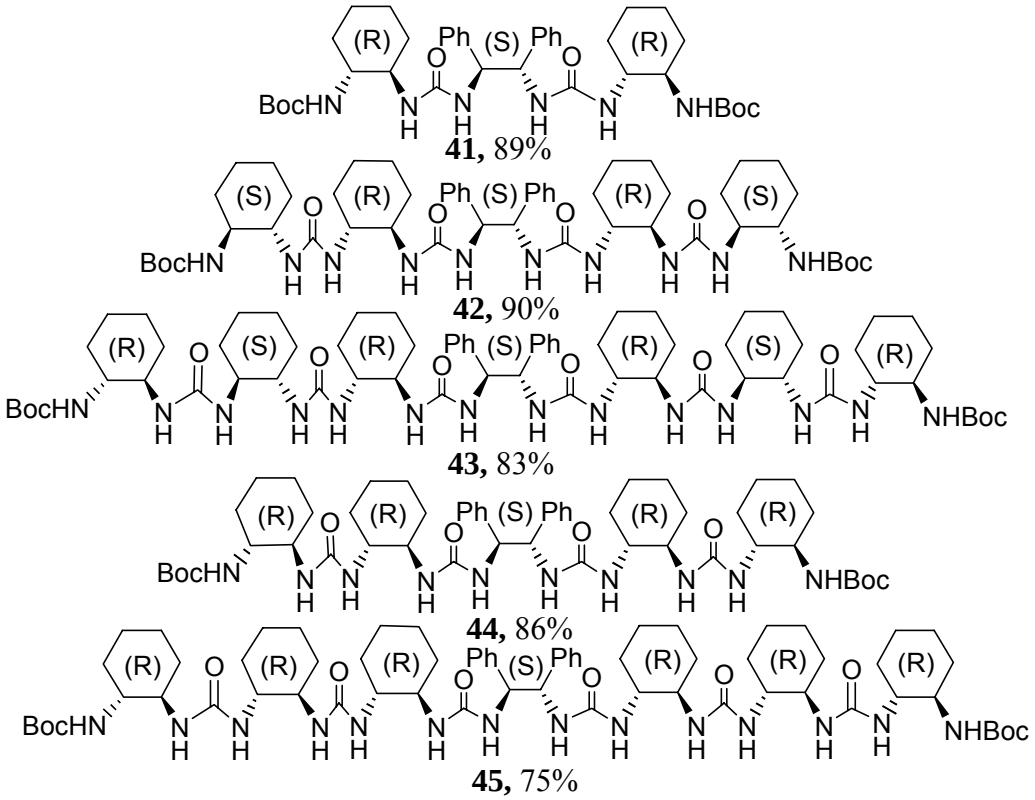


Figure 4.10 Heterochiral oligoureas based on DACH and DPEDA

Eventually, different combinations of monomers were obtained, both homochiral and heterochiral (**Figure 4.11**).

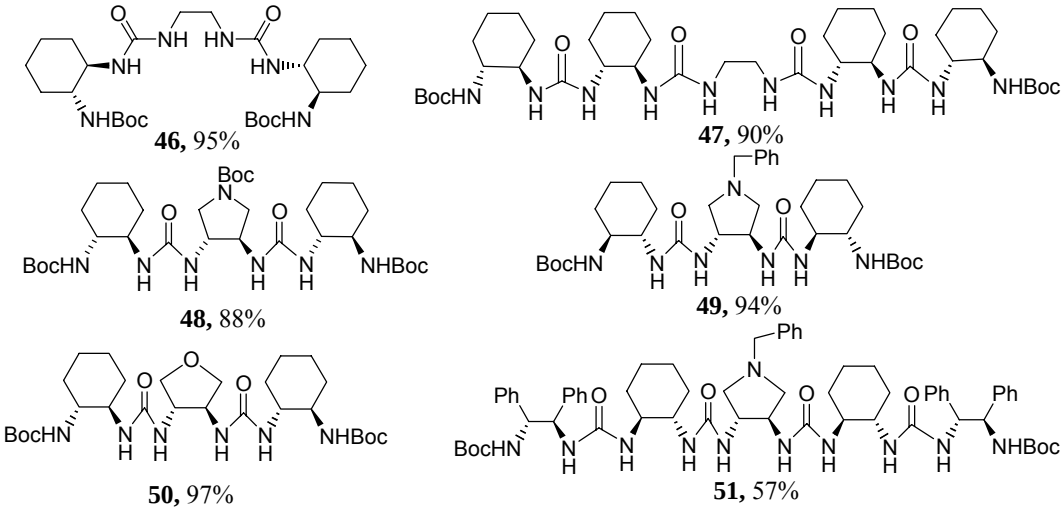


Figure 4. 11 Synthesis of other heterostructural oligoureas

4.3 Fragment condensation attempt

The syntheses above show that with compound **4** as an intermediate, growing a chain by adding one unit at a time in one direction or two units at a time in two directions is achievable. But it is also obvious that oligomer growth by this way is relatively inefficient. Compared with stepwise addition, fragment condensation is much more efficient because it has fewer steps and the purification is relatively easier. To achieve fragment condensation, two attempts were carried out at the same time.

Activation of compound **7** (**Figure 4.12**) was attempted, because activation of compound **7**, then dimerization of activated compound **7** and compound **8** would lead to differentially protected tetraurea. Removal of Tfa and activation of the monoprotected tetraurea would lead to the differentially protected octaurea. This would be the most efficient way to achieve the synthetic goal. Unfortunately, the activation of compound **7** failed. The reason was discovered in the second trial of fragment condensation.

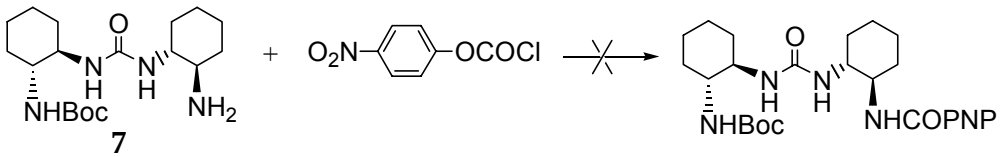


Figure 4. 12 Activation of monoprotected diurea

At the same time, compound **52** was synthesized to act as a linker for fragment condensation. Upon reacting **52** with **7**, instead of getting pentaurea **17**, compound **53** was obtained because of an intramolecular cyclization reaction (**Figure 4.13**).

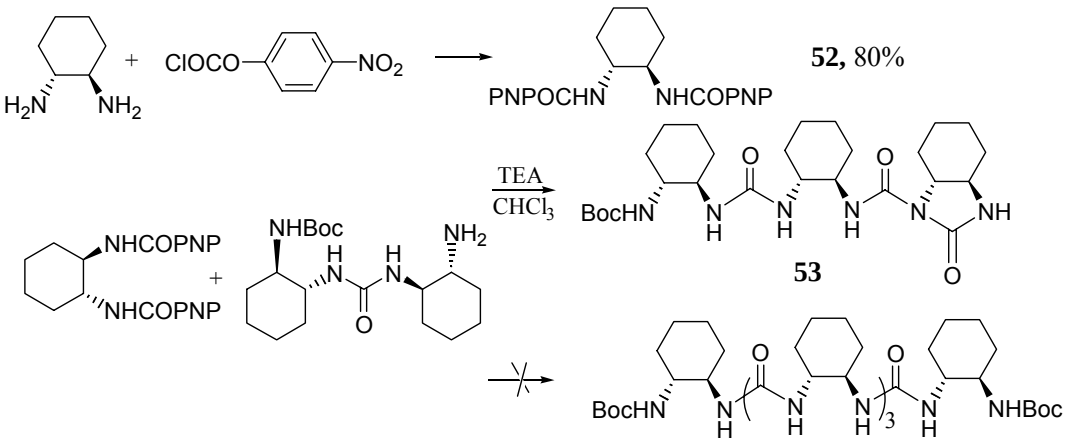


Figure 4.13 Fragment condensation attempt 1

Crystal structure of compound **53** (**Figure 4.14**) was obtained.

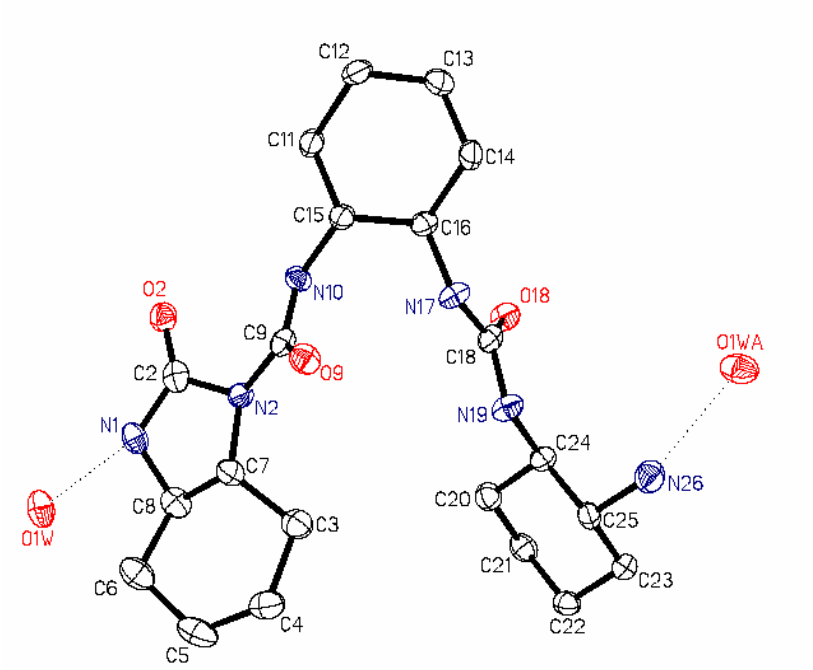


Figure 4.14 Crystal structure of cyclized triurea 53

Also the reaction between compound **7** and **54** led to cyclized compound **55** instead of pentaurea **37 (Figure 4.15).**

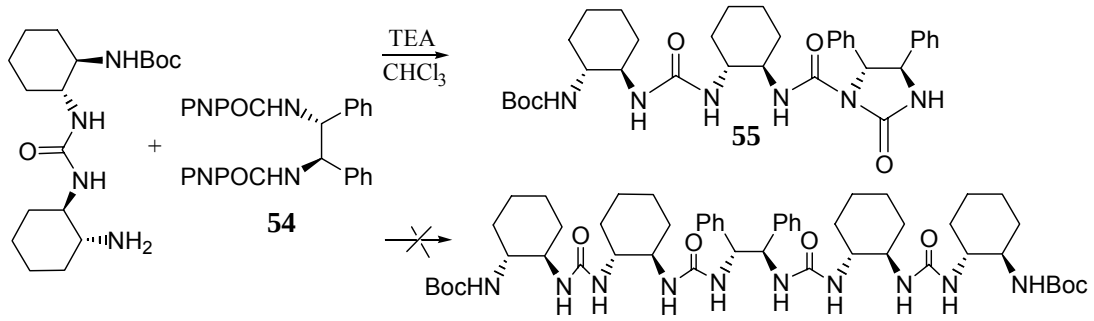


Figure 4.15 Fragment condensation attempt 2

The intermediate of the cyclization reaction may be an isocyanate. By protecting the amino groups, activation may be able to provide a protected and activated linker which may not cyclize when used as a linker, since the isocyanate pathway is blocked.

To test this hypothesis, a trial reaction was carried out. A secondary amine, dibenzylamine, was activated successfully, but the reaction of (1*R*, 2*R*)-*trans*-1, 2-diaminocyclohexane and activated dibenzylamine led to no desired product (**Figure 4.16**). Only both of the starting materials were recovered. That indicates the isocyanate intermediate is necessary for the activated compound to work. Currently, the fragment condensation does not work. Maybe another activating reagent could fulfill this goal.

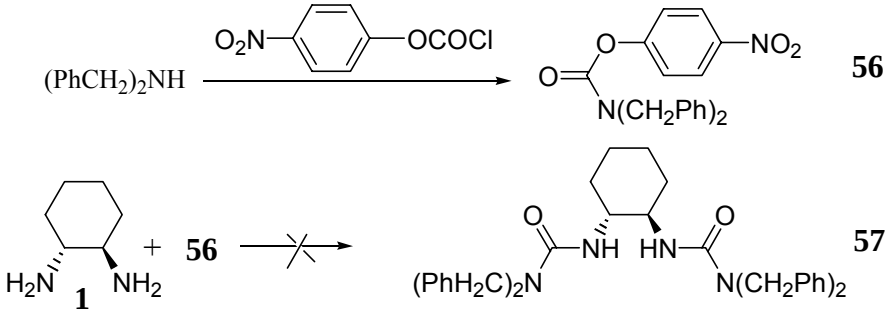


Figure 4.16 Mechanism exploration

4.4 Synthesis of an achiral diurea, some thioureas and a pseudopentaurea

To study the effect of the chirality of the chain on the global conformation of the molecule, an achiral diurea was synthesized, and at the same time, some thioureas were also synthesized (**Figure 4.17**).[10, 11] To grow crystals for protected RSR DACH-DPEDA-DACH, this compound was capped by cyclohexylamine, in actuality, a pseudopentaurea was synthesized and crystals were obtained.

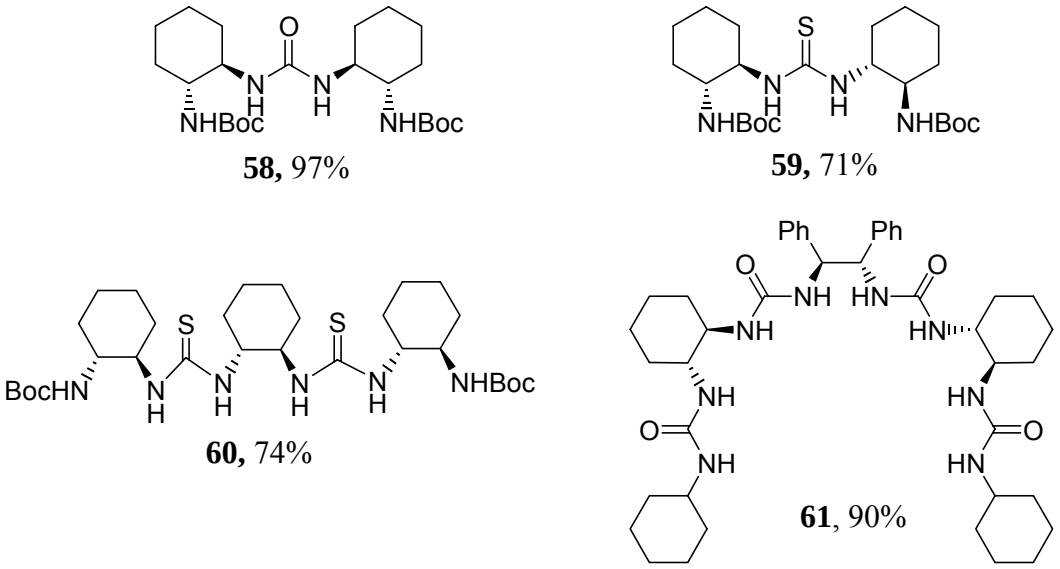


Figure 4.17 Other oligoureas

4.5 Synthesis section

4.5.1 Synthesis of 4-nitrophenyl-*N*-Boc-1,2-diaminocyclohexanecarbamate (4)

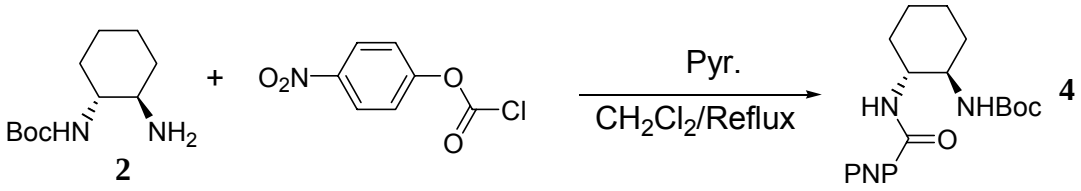


Figure 4.18 Synthesis of compound 4

Mono Boc-protected diamine **2** (0.31 g, 1.45 mmol) was dissolved in a mixture of dry CH_2Cl_2 (2.0 mL) and pyridine (0.11 g, 1.45 mmol). 4-Nitrophenyl chloroformate (0.29 g, 1.45 mmol) was added, and the solution was refluxed overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1 M $NaHCO_3$ solution, water and brine. The solution was dried (Na_2SO_4) and the solvent was removed under reduced pressure to yield the colorless product 0.48 g (yield, 87 %). It can be further purified by recrystallization with ethyl acetate.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (2H, m), 7.73 (2H, m), 5.95 (1H, d), 4.70 (1H, d) 3.37 (2H, m), 2.18 (1H, m), 2.04 (1H, m), 1.63 (2H, m), 1.45 (9H, s), 1.33 (4H,m); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 156.4, 155.5, 152.6, 143.9, 125.2, 122.0, 77.5, 54.8, 53.1, 31.9, 31.7, 28.3, 24.5, 24.4; MALDI (M) 379; IR (KBr) 3341 (s), 3086 (w), 2975 (w), 2936 (m), 2857 (w), 1722 (s),

1675 (s), 1646 (w), 1524 (s), 1429 (m), 1366 (w), 1349 (m), 1321 (m), 1279 (m), 1223 (m), 1206 (m), 1167(m); mp 149-152 °C.

4.5.2 Synthesis of Boc-(DACH)$_2$-Boc (5)

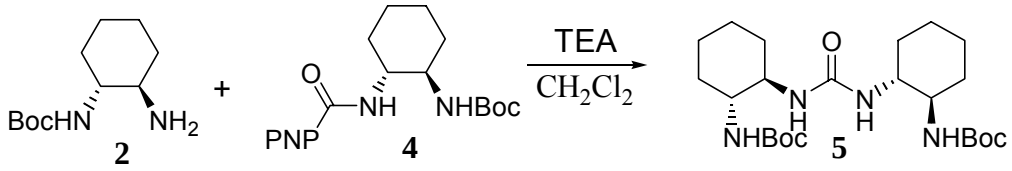


Figure 4.19 Synthesis of compound 5

Compound **4** (0.25 g, 0.66 mmol) was added to a solution of mono Boc-protected diamine **2** (0.11 g, 0.5 mmol) and TEA (100 µL, 0.72 mmol) in CH_2Cl_2 (10 mL), the reaction mixture was stirred at room temperature until compound **2** was consumed (as evidenced by TLC). The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with dilute aq. NaOH, water and brine. After drying (Na_2SO_4) and filtering, the solvent was removed under reduced pressure to give the colorless product 215 mg (yield: 93%). Crystals were grown in MeOH/EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (d, 2H, *J* = 7.6 Hz), 4.72 (d, 2H, *J* = 8.0 Hz), 3.44 (m, 2H), 3.25 (m, 2H), 2.00 (d, 2H), 1.70 (m, 2H), 1.41 (s, 18H), 1.25 (m, 8H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.6, 155.5, 77.4, 54.7, 52.4, 36.0, 24.4, 24.3, 28.2, 32.1; MALDI (MNa^+) 477; IR (KBr): 3334 (s), 2983 (w), 2933 (m), 2855 (w), 1688 (s), 1644 (s), 1558 (s), 1531 (s), 1389 (w), 1367 (w), 1321 (m), 1279 (m), 1176 (m), 1019 (w);

decomp. 245 °C.

4.5.3 Synthesis of Tfa-(DACH)$_2$-Boc (6)

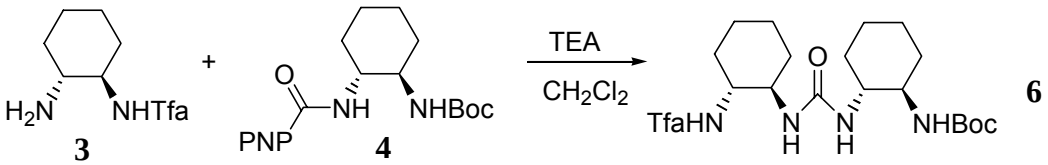


Figure 4.20 Synthesis of compound 6

Compound **4** (0.25 g, 0.66 mmol) was added to a solution of Tfa-protected diamine **3** (0.12 g, 0.54 mmol) and triethylamine (TEA) (100 µL, 0.72 mmol) in CH_2Cl_2 (10 mL), the mixture was stirred at room temperature until **3** was consumed (as evidenced by TLC). The reaction mixture was then diluted with CH_2Cl_2 (150 mL) and washed with diluted aq. NaOH, water and brine. After drying (Na_2SO_4) and filtration, the solvent was removed under reduced pressure to yield a white solid 0.19 g (yield, 95%). Crystals were grown in MeOH/EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (1H, d), 5.24 (1H, d), 4.72 (1H, d), 4.5 (1H, d), 3.62 (1H, d), 3.42 (1H, d), 3.35 (1H, m), 3.26(1H, m), 2.22 (1H, d), 1.95(2H, t), 1.82 (1H, d), 1.71 (8H, m), 1.43 (9H, s), 1.1-1.4 (8H, m); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.8, 156.2, 155.9, 155.7, 77.7, 55.1, 54.5, 52.7, 51.6, 32.6, 32.5, 32.3, 30.9, 28.4, 24.7, 24.5, 24.4, 24.2; MALDI (MNa^+) 473; IR (KBr) 3321 (s), 3276 (m), 2940 (s), 2856 (m), 1700 (s), 1685 (m), 1640 (s), 1450 (w), 1367 (w), 1322 (m), 1276 (w), 1181 (s); decomp. 243-245 °C.

4.5.4 Synthesis of Tfa-(DACH)$_3$-Boc (9)

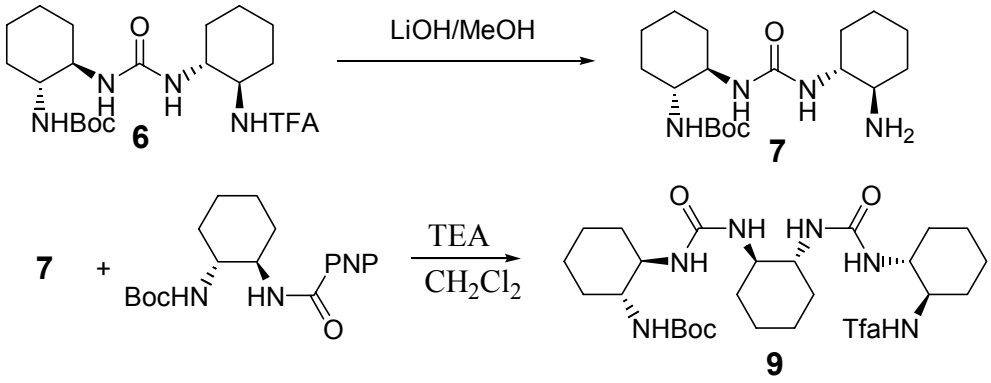


Figure 4.21 Synthesis of differentially protected triurea 9

To make compound **7**, the differentially protected diurea **6** (0.35 g, 0.78 mmol) was refluxed for 2h in 10 mL LiOH (112 mg, 4.68 mmol) in MeOH with 10% distilled water, and then the solvents were removed under reduced pressure. The residue was then dissolved with heating in EtOAc (20 mL) and distilled water (5 mL), The aqueous layer was removed and the organic layer was dried with Na_2SO_4 and then EtOAc was removed under reduced pressure to give the product 0.21 g (yield: 77%).

Compound **4** (0.25 g, 0.66 mmol) was added to a solution of Tfa-protected diurea **7** (0.21 g, 0.6 mmol) and triethylamine (TEA) (100 µL, 0.72 mmol) in CH_2Cl_2 (10 mL), the mixture was stirred at room temperature overnight. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with diluted aq. NaOH, water and brine. After drying (Na_2SO_4) and filtration, the solvent was removed under reduced pressure to yield a white solid 0.32 g (yield: 92%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.31 (d,1H, *J* = 6.8 Hz), 6.54 (d,1H, *J* = 7.2 Hz), 5.99 (d, 1H, *J* = 7.2 Hz), 5.86-5.80 (m, 3H), 3.60-3.19 (m, 5H), 3.00 (m, 1H), 1.85-1.82 (br, 6H), 1.64-1.34 (m, 6H), 1.34 (s, 9H), 1.21-1.03 (m, 12H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.6, 158.5, 156.0, 155.7, 155.5, 77.4, 55.5, 55.2, 52.9, 52.7, 52.2, 51.4, 32.6, 32.3, 32.2, 30.7, 28.3, 24.6,

24.3, 24.2, 24.0; MALDI (MNa^+) 613; IR (KBr) 3410 (s), 2934 (m), 1702 (s), 1684 (s), 1639 (s), 1572 (s), 1185 (s), 1168 (s); decomp. 250 °C.

4.5.5 Synthesis of Tfa-$(DACH)_4$-Boc (11)

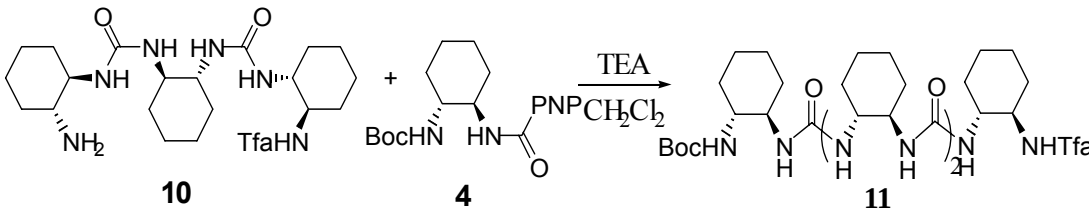


Figure 4.22 Synthesis of differentially protected tetraurea 11

Compound **4** (0.2 g, 0.53 mmol) was added to a solution of Tfa-protected triurea (0.25 g, 0.52 mmol) and triethylamine (TEA) (100 µL, 0.72 mmol) in MeOH (10 mL), the mixture was refluxed overnight. The product was recovered by filtration followed by washing with EtOAc. Recrystallization in EtOAc/MeOH gave a white solid 0.35 g (yield, 94%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.35 (d, 1H), 6.56 (d, 1H), 6.10 (d, 1H), 5.87 (m, 5H), 1.34 (s, 9H); ^{13}C NMR was not obtained because of the poor solubility; MALDI (MNa^+) 753; IR (KBr) 3463 (s), 1637 (m); decomp. 225 °C.

4.5.6 Synthesis of DACH triureas (12) and (13)

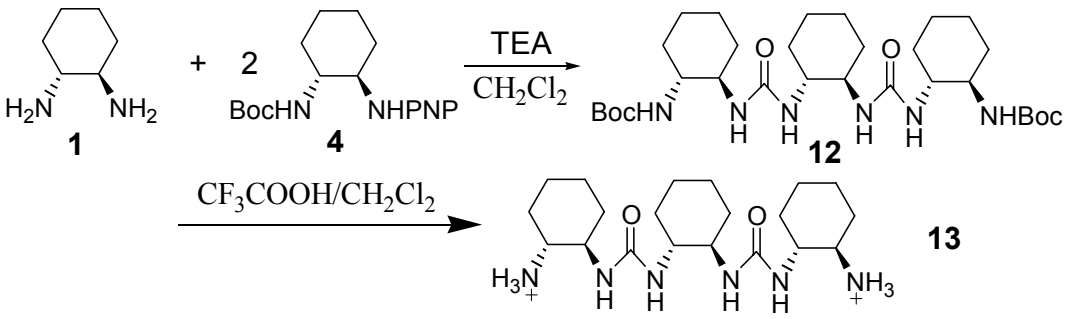


Figure 4.23 Synthesis of triureas 12 and 13

Compound **4** (800 mg, 2.1 mmol) was added to a solution of **1** (120 mg, 1.05 mmol) and triethylamine (300 µL) in CH_2Cl_2 (7 mL). The mixture was stirred at room temperature until **4** was consumed (as evidenced by TLC). The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with dilute aq. NaOH, water and brine. After drying (Na_2SO_4) and filtering, the solvent was removed under reduced pressure to yield the colorless product 0.58 g (yield: 92 %). It can be further purified by recrystallization with methanol. Crystals were growth in $MeOH/H_2O$.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.55 (2H, d, *J* = 7.2 Hz), 5.87 (2H, d, *J* = 6.4 Hz), 5.84 (d, 2H, *J* = 8.4 Hz), 3.33-3.19 (m, 4H), 3.00 (m, 2H), 1.90-1.81 (m, 6H), 1.58 (br, 6H), 1.35 (18H, s), 1.19-1.07 (12H, m); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.5, 155.4, 77.4, 55.2, 52.8, 52.2, 32.5, 32.2, 28.2, 24.5, 24.2; MALDI (MNa^+) 617; IR (KBr) 3320 (s), 2932 (s), 2855 (m), 1686 (s), 1636 (s), 1577 (s), 1529 (s), 1319 (m), 1175 (m); mp 253 °C (decompose).

Into a 5 mL round-bottom flask equipped with a magnetic stirrer was added Boc protected triurea **12** (600 mg, 1 mmol), CH_2Cl_2 (1 mL), and trifuoroacetic acid (300 μL, 3.5 mmol). The flask was fitted with a septum, and the solution was stirred at room temperature overnight. After the reaction, the solvent was removed under reduced pressure, the deprotected triurea **13** was obtained as a salt (yield: 100%). Crystals was grown in MeOH.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.83 (br, 6H), 6.19 (d, 2H, *J* = 7.2Hz), 6.03 (d, 2H, 6.8), 3.43-3.26 (m, 4H), 2.76 (dt, 2H), 1.98-1.62 (m, 12H), 1.35-1.16 (m, 12H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.2, 54.2, 53.2, 51.2, 32.3, 31.881, 29.5, 24.4, 24.2, 23.4; MALDI (MNa^+) 417; IR (KBr) 3415 (s), 2940 (m), 2864 (w), 1680 (s), 1638 (s), 1570 (m), 1204 (s), 1138 (m); decomp. the compound changed color at around 170 °C, and became a black liquid at around 192 °C.

4.5.7 Deprotection of Boc-(DACH)$_2$-Boc (14)

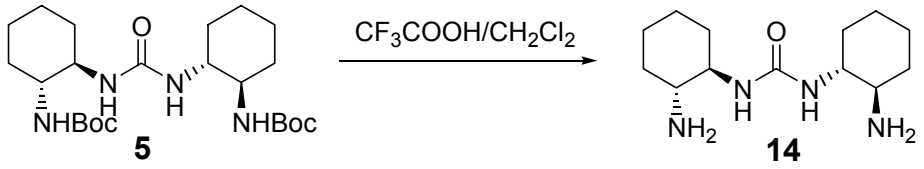


Figure 4.24 Deprotection of Boc protected diurea

Into a 5 mL round-bottom flask equipped with a magnetic stirrer was added Boc- protected diurea **5** (450 mg, 1 mmol), CH_2Cl_2 (1 mL), and CF_3COOH (250 μL, 3.24 mmol). The flask was fitted with a septum, and the solution was stirred at room temperature overnight. The solution was then poured into ether (100 mL) and washed with 10% aqueous NaOH and saturated aqueous NaCl. The colorless solution was then dried (Na_2SO_4) and concentrated in vacuo to provide 240 mg while solid **14** (yield: 95%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.26 (d, 2H), 3.35 (m, 2H), 2.76 (m, 2H), 2.00-1.60 (m, 8H), 1.40-1.10 (m, 8H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.6, 158.3, 54.5, 51.4, 48.6, 31.5, 29.4, 28.3, 24.3, 23.4; MALDI (MH^+) 255, (MNa^+) 277; IR (KBr) 3446 (s), 2945 (w), 1674 (s), 1204

(m), 1140 (m); decomp. the compound changed color at around 198 °C, and became a black liquid at around 204 °C.

4.5.8 Synthesis of all R DACH tetraureas (15) and (16)

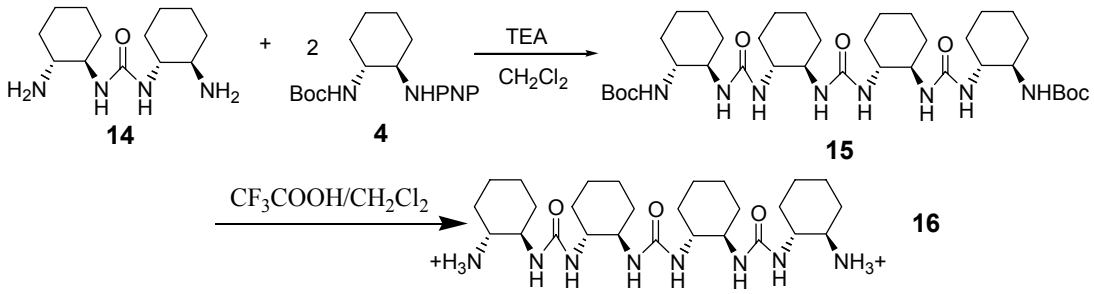


Figure 4.25 Synthesis of tetraureas 15 and 16

Compound **4** (760mg, 2 mmol) was added to a solution of **14** (0.25 g, 1 mmol) and TEA (280 μL, 2 mmol) in MeOH (10 mL), the reaction mixture was refluxed overnight. The product **15** was recovered by filtration followed by washing with EtOAc. Recrystallization in MeOH/EtOAc gave colorless solid 0.57 g (yield: 91%).

Compound **15**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.58 (d, 2H), 5.82 (m, 6H), 3.40-3.20 (m, 6H), 3.00 (m, 2H), 1.95-1.75 (m, 8H), 1.60 (br, 8H), 1.34 (s, 18H), 1.30-1.00 (m, 16H); ^{13}C NMR was not obtained because of the poor solubility of this compound; MALDI (MNa^{+}) 757; IR (KBr) 3416 (s), 2932 (w), 2856 (w), 1685 (w), 1637 (m) , decomp. 265 °C.

Following procedure **4.5.6**, the deprotected tetraurea **16** was recovered as a salt (yield: 100%).

Compound **16**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.77 (br, 6H), 6.02 (d, 2H, J = 8.4Hz), 5.93 (d, 2H, J = 7.6 Hz), 5.85 (d, 2H, J = 8.0 Hz), 3.41 (m, 2H), 3.30 (m, 2H), 3.16 (m, 2H), 3.20 (m, 2H), 2.66 (dt, 2H), 1.89-1.79 (m, 8H), 1.64-1.60 (m, 8H), 1.24-1.10 (m, 16H); ^{13}C NMR (400 MHz, CD_3OD) δ 160.9, 57.0, 55.7, 54.9, 53.2, 34.3, 33.8, 33.5, 31.2, 26.0, 25.8, 25.1; MALDI (MNa^{+}) 557; IR (KBr) 3413 (s), 2937 (m), 2860 (w), 1677 (s), 1638 (s), 1619 (s), 1587 (m), 1203 (m), 1136 (m); decomp. the compound changed color at about 195 °C, and became black over 200 °C.

4.5.9 Synthesis of all R DACH pentaureas (17) and (18)

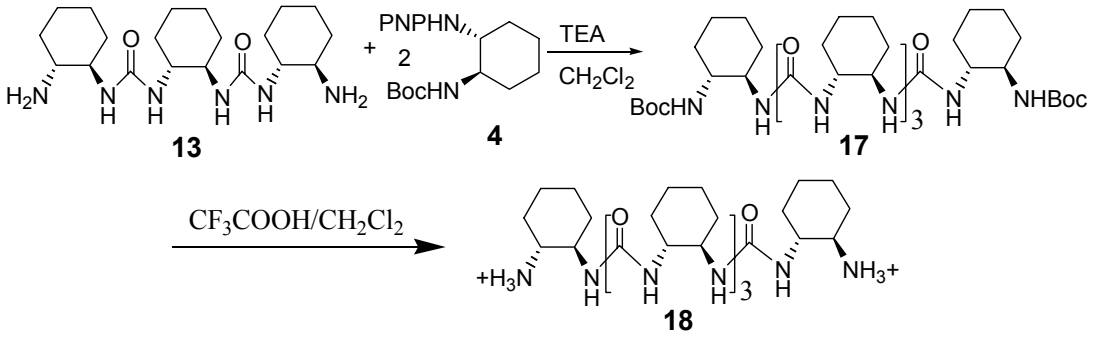


Figure 4.26 Synthesis of pentaureas 17 and 18

Following procedure **4.5.8**, compound **17** was obtained as a colorless solid (yield: 87%)

Compound **17**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.55 (d, 2H), 5.85 (m, 8H), 3.40-3.20 (m, 8H), 3.00 (m, 2H), 1.94-1.46 (m, 20H), 1.35 (s, 18H), 1.26-1.00 (br, 20H); ^{13}C NMR was not obtained because of the poor solubility; MALDI (MNa^+) 897.6; IR (KBr) 3334 (s), 2930 (s), 2855 (m), 1685 (m), 1635 (s), 1558 (m), 1539 (m); decomp. 250 °C.

Following procedure **4.5.6**, the deprotected pentaurea **18** was recovered as a salt (yield: 100%).

Compound **18**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.76 (d, 6H), 6.06 (d, 2H, J = 8.0 Hz), 5.98 (d, 2H, J = 7.6 Hz), 5.87 (m, 4H), 3.40 (m, 2H), 3.32 (m, 2H), 3.21 (m, 2H), 3.14 (m, 2H), 2.77 (m, 2H), 1.94-1.77 (m, 10H), 1.64-1.59 (m, 10H), 1.40-1.00 (m, 20H); ^{13}C NMR (DMSO-*d6*) δ 158.2, 158.1, 54.4, 53.9, 52.8, 52.4, 51.1, 32.4, 32.3 (br), 31.8, 29.5, 24.4 (br), 24.2, 24.1, 23.3; MALDI (MNa^+) 698; IR (KBr) 3429 (s), 2935 (m), 2858 (w), 1638 (s), 1597 (m), 1204 (m), 1137 (m); decomp. 210 °C.

4.5.10 Synthesis of all R DACH hexaureas (19) and (20)

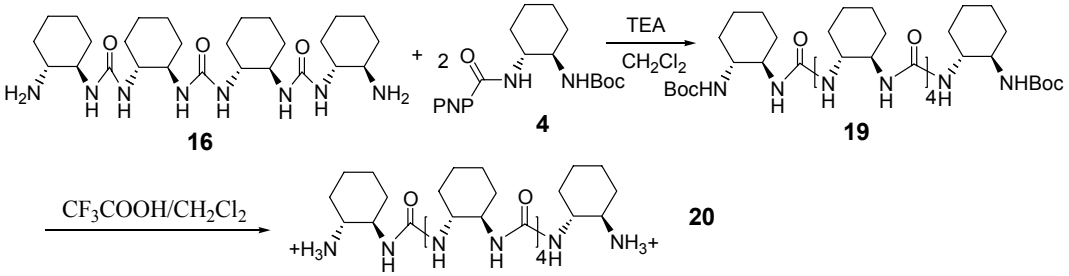


Figure 4.27 Synthesis of hexaureas 19 and 20

Following procedure **4.5.8**, compound **19** was obtained as a colorless solid and purified by column (yield: 87%), and **20** was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Compound **19**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.55 (d, 2H), 5.84 (br, 10H), 3.19 (br, 10H), 2.67 (m, 2H), 1.84 (br, 12H), 1.58 (br, 12H), 1.35 (s, 18H), 1.19-1.06 (br, 24H); ^{13}C NMR was not obtained because of its poor solubility; IR (KBr) 3338 (s), 2931 (s), 2856 (m), 1685 (m), 1637 (s), 1560 (s); decomp. 250 °C.

Compound **20**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.76 (d, 6H), 6.07 (d, 2H, *J* = 8.0 Hz), 5.98 (d, 2H, *J* = 6.8 Hz), 5.87 (d, 6H), 3.44-3.11 (m, 10H), 2.75 (m, 2H), 1.91-1.77 (m, 12H), 1.64-1.58 (m, 12H), 1.40-1.03 (m, 24H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.4, 158.3, 54.6, 54.2, 51.2, 32.7 (br), 31.9, 29.6, 24.5 (br), 24.3, 23.5; MALDI (MNa^{+}) 837; IR (KBr) 3339 (s), 2934 (s), 2857 (m), 1643 (s), 1599 (s), 1203 (s), 1136 (s); decomp. the compound changed color at 190 °C, and became black at around 200 °C.

4.5.11 Synthesis of all R DACH heptaureas (21) and (22)

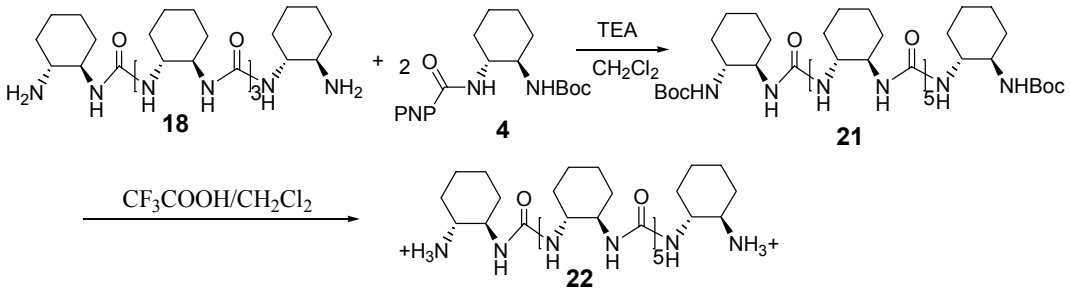


Figure 4.28 Synthesis of heptaureas 21 and 22

Following procedure **4.5.8**, compound **21** was obtained as a colorless solid and purified by column (yield: 80%), and compound **22** was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Compound **21**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.90 (d, 2H), 5.86 (br, 12H), 3.22-314 (m, br, 12H), 2.67 (m, 2H), 1.84-1.60 (m, br, 28 H), 1.35 (s, 18H), 1.22-1.04 (m, br, 28); IR (KBr) 3414 (s), 2930 (m), 2855 (w), 1646 (s), 1560 (m); decomp. the compound changed color at around 240 °C.

Compound **22**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.74 (br, 6H0, 6.03 (d, 2H), 5.95 (d, 2H), 5.85 (br, 8H), 3.48-3.05 (m, 12H), 2.71 (m, 2H), 1.96-1.48 (m, 28H), 1.40-1.00 (m, 28H); ^{13}C NMR was not obtained because of its poor solubility; MALDI (MNa^{+}) 978; IR (KBr) 3463 (s), 1638 (w), 1097 (s); decomp. 202 °C.

4.5.12 Synthesis of all R DACH octaureas (23) and (24)

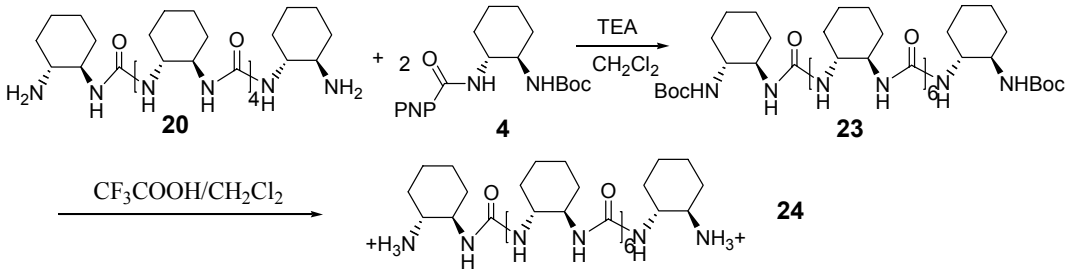


Figure 4.29 Synthesis of octaureas 23 and 24

Following procedure **4.5.8**, compound **23** was obtained as a colorless solid and purified by column (yield: 77%), and compound **24** was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Compound **23** was not characterized, but it was confirmed by the characterization of the deprotected form compound **24**.

Compound **24**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.74 (br, 6H), 6.04 (d, 2H), 5.94 (d, 2H), 5.85 (br, 10H), 3.56-3.12 (m, br, 14H), 2.70 (m, 2H), 1.96-1.52 (m, br, 32 H), 1.44-1.04 (m, br, 32 H); ^{13}C NMR was not obtained because of its poor solubility; MALDI (MNa^{+}) 1118; IR (KBr) 3405 (s), 2932 (m), 2857 (w), 1654 (s), 1203 (m); decomp. 210 °C.

4.5.13 Synthesis of all R DACH nonaureas (25) and (26)

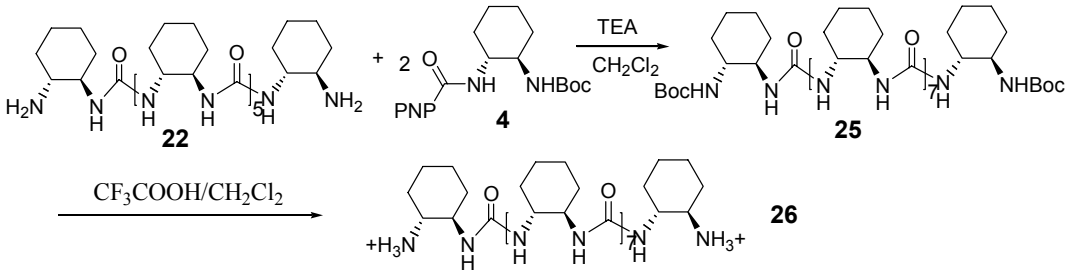


Figure 4.30 Synthesis of nonaureas 25 and 26

Following procedure **4.5.8**, compound **25** was obtained as a colorless solid and purified by column (yield: 70%), and compound **26** was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Compound **25** was not characterized, but it was confirmed by the characterization of the deprotected form compound **26**.

Compound **26**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.73 (br, 6H), 6.03 (d, 2H), 5.96 (d, 2H), 5.85 (br, 12H), 3.42-3.16 (m, br, 16H), 1.84-1.57 (m, br, 36 H), 1.38-1.54 (m, br, 36 H); ^{13}C NMR

was not obtained because of its poor solubility; MALDI (MNa^+) 1258; IR (KBr) 3414 (s), 2936 (m), 1638 (m), 1618 (m); decomp. 215 °C.

4.5.14 Synthesis of RSR DACH triurea (27)

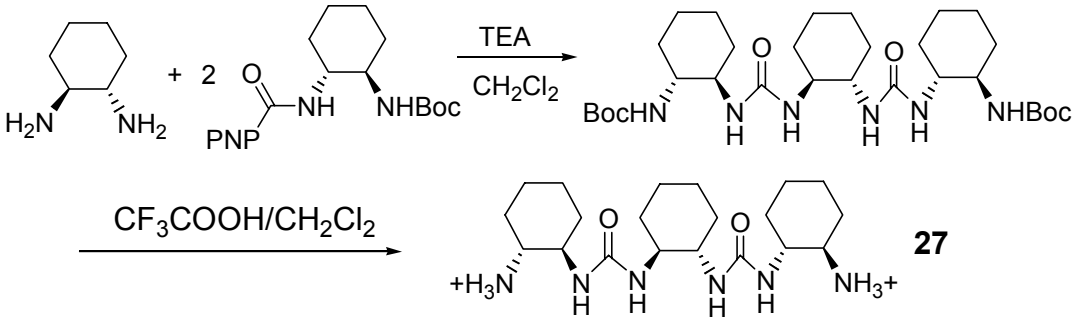


Figure 4.31 Synthesis of RSR triurea 27

Following procedure **4.5.2**, Boc-protected RSR triurea was obtained as a colorless solid (yield: 95%), and **27** was obtained as a salt by following procedure **4.5.6** (yield: 100%). Crystals of **27** were grown in MeOH.

Boc-protected form of compound **27**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.59 (d, 2H, *J* = 7.2 Hz), 5.92 (d, 2H, *J* = 5.6 Hz), 5.73 (d, 2H, *J* = 6.8 Hz), 3.22 (m, 4H), 3.10 (b, 2H), 1.83 (b, 6H) 1.58-1.52 (br, 6H), 1.36 (s, 18H), 1.23-1.14 (m, 12H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 157.9, 155.4, 77.4, 53.9, 52.4, 51.5, 32.4, 31.9, 30.1, 28.2, 24.2, 24.1, 23.0; IR (KBr) 3333 (s), 2931 (s), 2856 (m), 1682 (s), 1633 (s), 1554 (s), 1320 (m), 1173 (m); decomp. 206-210 °C.

Compound **27**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.77 (br, 6H), 6.18 (d, 4H), 3.30 (m, 4H), 2.80 (m, 2H), 1.97-1.56 (m, 12H), 1.40-1.21 (m, 12H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 170.4, 158.4, 59.8, 54.8, 51.3, 31.4, 29.4, 24.2, 23.3, 20.8, 14.1; MALDI (MNa^+) 417; IR (KBr) 3443 (s), 2930 (m), 2860 (w), 1665 (s), 1571 (m), 1203 (m); decomp. 205-212 °C.

4.5.15 Synthesis of SRSRS DACH pentaurea (28)

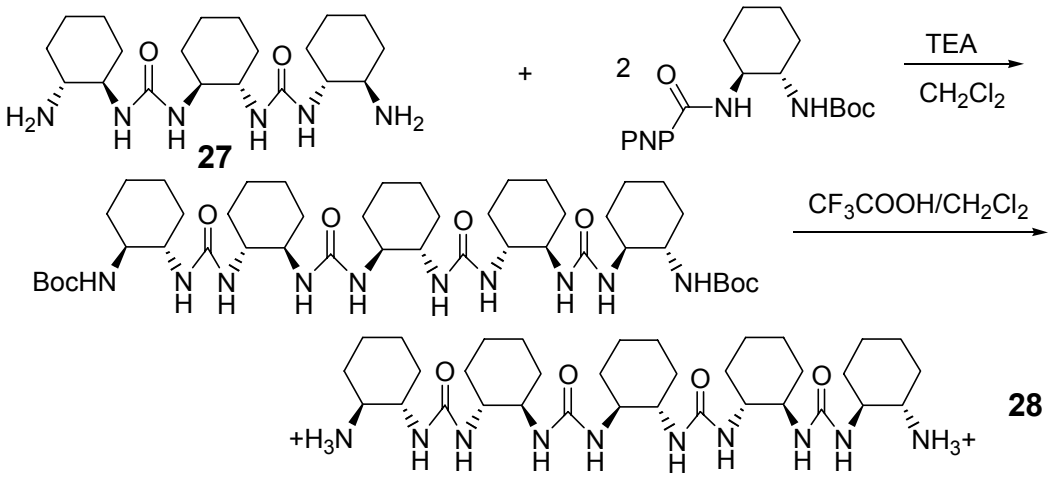


Figure 4.32 Synthesis of SRSRS DACH pentaurea

Following procedure **4.5.2**, Boc-protected SRSRS pentaurea was obtained as a colorless solid and purified by column (yield: 94%), and compound **28** was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Boc-protected form of compound **28**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.60 (d, 2H), 5.96 (d, 2H), 5.93-5.83 (m, 4H), 5.762 (d, 2H), 3.21 (m, 8H), 3.10 (m, 2H), 1.83 (br, 10H), 1.58 (br, 10H), 1.36 (s, 18H), 1.30-1.00 (br, 10H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.0, 157.9, 155.4, 77.5, 53.8, 52.5 (m), 32.6, 32.1, 31.4 (m), 28.3, 24.2 (m), 23.5 (m); IR (KBr) 3343 (s), 2932 (s), 2856 (m), 1683 (s), 1634 (s), 1560 (s); decomp. 218 °C.

Compound **28**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.85 (br, 6H), 6.14 (m, 6H), 5.95 (br, 2H), 3.30 (m, 8H), 2.82 (m, 2H), 1.99-1.56 (m, 20H), 1.40-1.15 (m, 20H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 159.0, 158.4, 55.0, 54.0, 53.2, 52.1, 51.6, 31.5 (m), 29.6, 29.5, 24.2, 23.5 (m); MALDI (MNa^{+}) 697; IR (KBr) 3413 (s), 2938 (m), 2862 (w), 1638 (s), 1570 (m), 1204 (m), 1138 (m); mp 178-181 °C.

4.5.16 Synthesis of RSRSRSR DACH heptaurea (29)

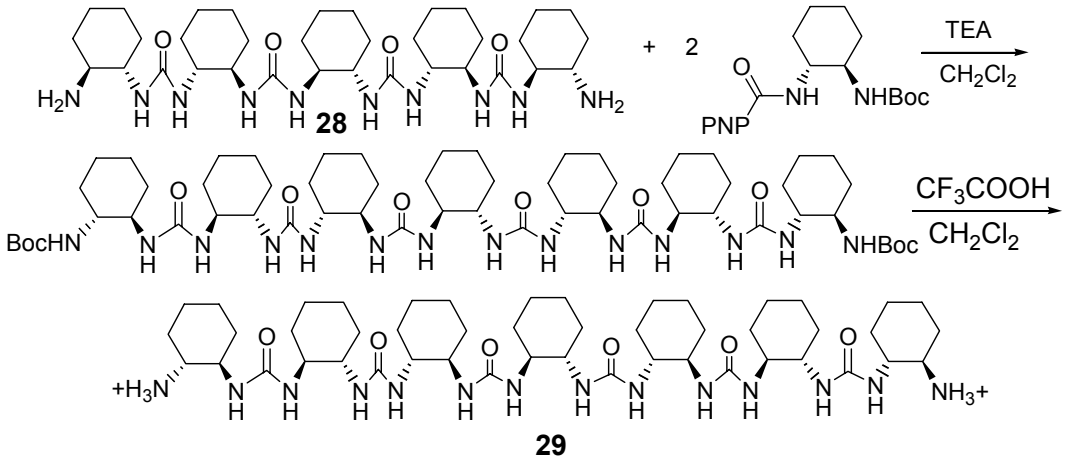


Figure 4.33 Synthesis of alternate RS heptaurea

Following procedure **4.5.2**, Boc protected RSRSRSR heptaurea was obtained as a colorless solid and purified by column (yield: 88%), and **29** was obtained as a salt by following procedure **4.5.6** and further purified by HPLC (yield: 100%).

Boc-protected form of compound **29**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.59 (d, 2H), 6.05-5.75 (m, 12H), 4.46-3.06 (m, 14H), 1.87 (br, 14H), 1.56 (br, 14H), 1.37 (s, 18H), 1.26-1.04 (br, 28H); IR (KBr) 3414 (s), 2925 (w), 1638 (m), 1618 (m); mp: 232 °C.

Compound **29**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.83 (br, 6H), 6.40-5.80 (m, br, 12H), 3.60-3.04 (m, br, 12H), 2.82 (m, 2H), 2.04-1.42 (m, br, 28H), 1.40-1.00 (m, br, 28H); ^{13}C NMR (DMSO-*d6*) δ 158.1 (br), 52.6 (br), 51.5, 31.5 (br), 29.5, 24.2, 23.4, 23.8 (br); MALDI (MNa^{+}) 978; IR (KBr) 3439 (s), 2934 (m), 2859 (w), 1630 (s), 1570 (s), 1204 (m); decomp.195-198 °C.

4.5.17 Synthesis of SRSRSRSRS DACH nonaurea (30)

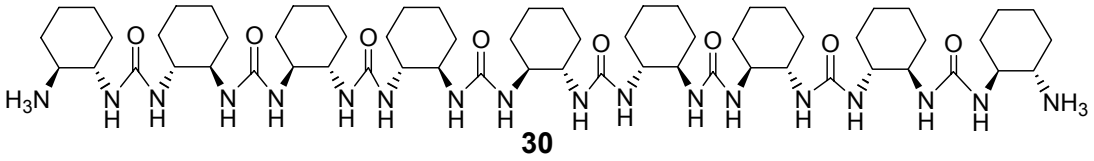


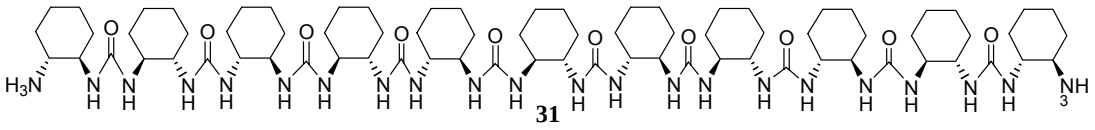
Figure 4.34 Alternate RS nonaurea 30

Following procedure **4.5.2**, Boc protected SRSRSRSRS nonaurea was obtained as a colorless solid and purified by column (yield: 70%), and compound **30** was obtained as a salt by following procedure **4.5.6** and further purified by HPLC (yield: 100%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.80 (br, 6H), 6.20-5.82 (m, br, 16H), 3.54-3.08 (m, br, 16H), 2.82 (m, 2H), 1.93-1.40 (m, br, 36H), 1.33-1.00 (m, br, 36H); ^{13}C NMR was not obtained

because of its poor solubility; MALDI (MNa^+) 1257; IR (KBr) 3448 (s), 2933 (w), 1636 (m), 1559 (w); decomp. 175 °C.

4.5.18 Synthesis of RSRSRSRSRSR undecaurea (31)



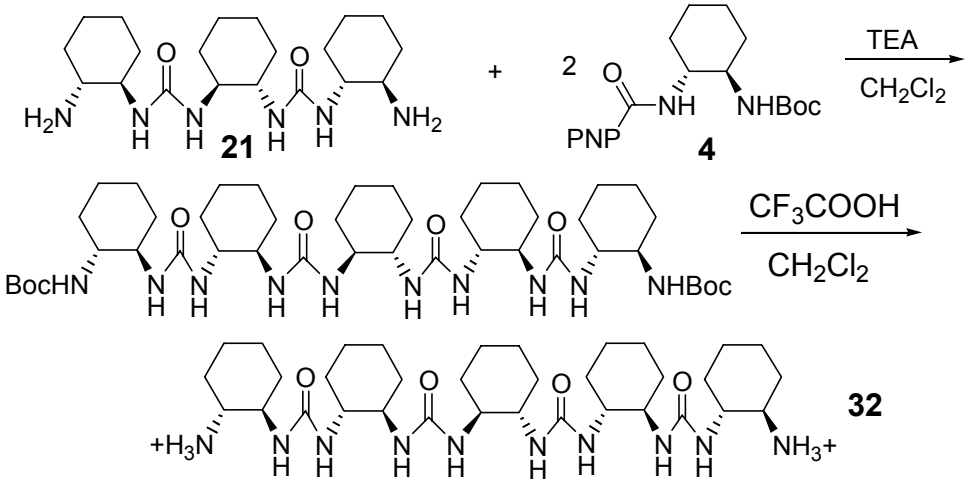
31

Figure 4.35 Alternate RS undecaurea

Following procedure **4.5.2**, Boc protected RSRSRSRSRSR undecaurea was obtained as a colorless solid and purified by column (yield: 72%), and compound **31** was obtained as a salt by following procedure **4.5.6** and further purified by HPLC (yield: 100%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.84 (br, 6H), 6.26-5.80 (m, br, 20H), 3.56-3.12 (m, br, 20H), 2.86 (m, 2H), 1.98-1.43 (m, br, 44H), 1.32-1.03 (m, br, 44H); ^{13}C NMR was not obtained because of its poor solubility; MALDI (MNa^+) 1258; IR (KBr) 3428 (s), 2933 (m), 2857 (w), 1635 (s), 1569 (s), 1204 (m); decomp.190 °C.

4.5.19 Synthesis of RRSRR DACH pentaurea (32)



21 **4** **32**

Figure 4.36 Synthesis of RRSRR pentaurea

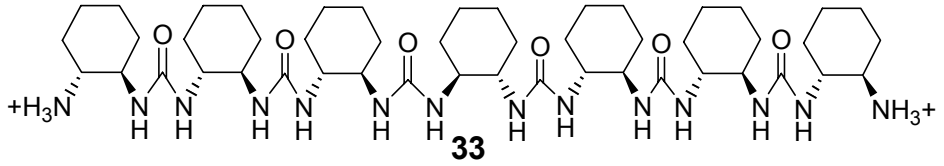
Following procedure **4.5.2**, Boc-protected RRSRR pentaurea was obtained as a colorless solid and purified by column (yield: 90%), and **32** was obtained as a salt by following procedure **4.5.6** and further purified by HPLC (yield: 100%).

Boc-protected form of compound **32**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.53 (d, 2H), 5.89 (br, 8H), 3.40-3.12 (m, 8H), 3.03 (m, 2H), 1.98-1.46 (m, 20H), 1.35 (s, 18H), 1.26-1.02 (m, 20H);

^{13}C NMR was not obtained because of its poor solubility; IR (KBr) 3412 (s), 2932 (s), 2856 (m), 1686 (m), 1636 (s), 1561 (s), 1174 (m); decomp. 223 °C.

Compound **32**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.78 (s, 6H), 6.07-5.94 (m, 8H), 3.43-3.08 (m, 8H), 2.78 (m, 2H), 1.95-1.40 (m, 20H), 1.40-1.15 (m, 20H); ^{13}C NMR (DMSO-*d6*) δ 158.1, 54.4, 51.0, 31.8, 29.5, 24.3, 23.4; MALDI (MNa^{+}) 697; IR (KBr) 3388 (s), 2938 (s), 2863 (m), 1678 (s), 1639 (s), 1567 (s), 1204 (s), 1137 (s); mp 178-180 °C.

4.5.20 Synthesis of RRRSRRR DACH heptaurea (33)



33

Figure 4.37 RRRSRRR heptaurea 33

Following procedure **4.5.2**, Boc protected RRRSRRR heptaurea was obtained as a colorless solid and purified by column (yield: 87%), and **33** was obtained as a salt by following procedure **4.5.6** and further purified by HPLC (yield: 100%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.81 (br, 6H), 6.09-5.89 (m, br, 12H), 3.38-3.09 (m, br, 12H), 2.74 (m, 2H), 1.95-1.59 (m, br, 28H), 1.35-1.15 (m, br, 28H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.3, 158.1, 158.0, 54.5, 54.0, 52.5, 51.1, 51.0, 32.4, 31.9, 31.7, 29.5, 24.4, 24.3, 23.4; MALDI (MNa^{+}) 978; IR (KBr) 3443 (s), 2935 (m), 1637 (m), 1578 (m), 1204 (w); decomp. the compound changed color at around 170 °C, and became a black liquid at around 185 °C.

4.5.21 Synthesis of all R triureas based on DACH and DPEDA (35) and (36)

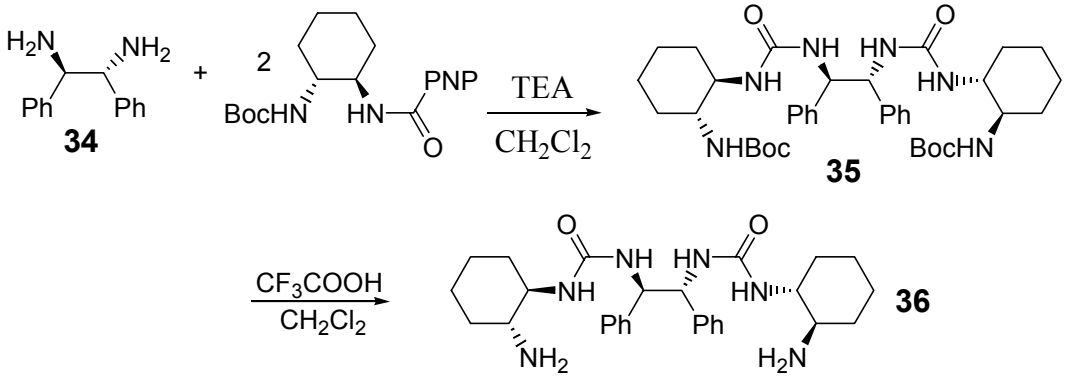


Figure 4.38 Synthesis of all R triureas based on DACH and DPEDA

Compound **4** (200 mg, 0.53 mmol) was added to a solution of **34** (50 mg, 0.24 mmol) and TEA (100 μL, 0.72 mmol) in CH_2Cl_2 (5 mL), the reaction mixture was refluxed overnight. The

reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with dilute aq. NaOH, water and brine. After drying (Na_2SO_4) and filtering, the solvent was removed under reduced pressure to give the colorless product.150 mg (yield: 92%). Crystals were grown in MeOH.

Compound **35**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.14-7.09 (m, 6H), 6.99-6.97 (d, 4H), 6.54-6.53 (d, 4H), 5.85 (d, 2H, J=6.8Hz), 4.84 (d, 2H, J = 4.4 Hz), 3.21 (m, 2H), 3.01 (m, 2H), 1.82 (m, 4H), 1.57 (br, 4H), 1.25 (s, 18H), 1.14-1.00 (m, 8H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 157.6, 155.5, 141.4, 127.6, 127.3, 126.5, 77.3, 58.5, 54.1, 52.6, 32.2, 32.8, 28.1, 24.4, 24.3; MALD I (MNa^+) 715; IR (KBr) 3361 (s), 3031 (w), 2977 (w), 2932 (s), 2857 (m), 1683 (s), 1646 (s), 1558 (s), 1527 (s), 1172 (s); mp 218-220 °C.

Triurea **35** (0.25 g, 0.36 mmol), CH_2Cl_2 (600 μL), and CF_3COOH (600 μL, 7.8 mmol) was added to a 5 mL round bottom flask. The flask was fitted with a septum, and the solution was stirred at room temperature overnight. Then the solvents were removed under reduced pressure, the residue was dissolved in 100 mL CH_2Cl_2, and the solution was washed with 5 mL of 1mol NaOH and 10 mL brine in turn. The colorless solution was then dried (Na_2SO_4) and concentrated in vacuo to provide 0.17 g (yield: 97%) deprotected triurea **36**. Crystals were grown in MeOH.

Compound **36**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.75 (s, 6H), 7.20-7.14 (m, 6H), 7.09-7.06 (m, 4H), 6.74 (d, 2H, *J* = 8 Hz), 6.19 (d, 2H, *J* = 8.4 Hz), 4.97 (d, 2H, *J* = 8.0 Hz), 3.42 (m, 2H), 2.78 (m, 2H), 2.00-1.64 (m, 8H), 1.40-1.10 (m, 8H); ^{13}C NMR (400 MHz, CD_3OD) δ 160.5, 141.5, 129.3, 128.7, 128.4, 60.9, 56.5, 53.4, 33.5, 31.2, 25.7, 25.0; MALD I (MNa^+) 515; IR (KBr) 3433, 3033 (w), 2941 (m), 1676 (s), 1560 (m), 1204 (s), 1137 (m); decomp. 165-168 °C.

4.5.22 Synthesis of all R pentaurea $(DACH)_2$-DPEDA-$(DACH)_2$ (37)

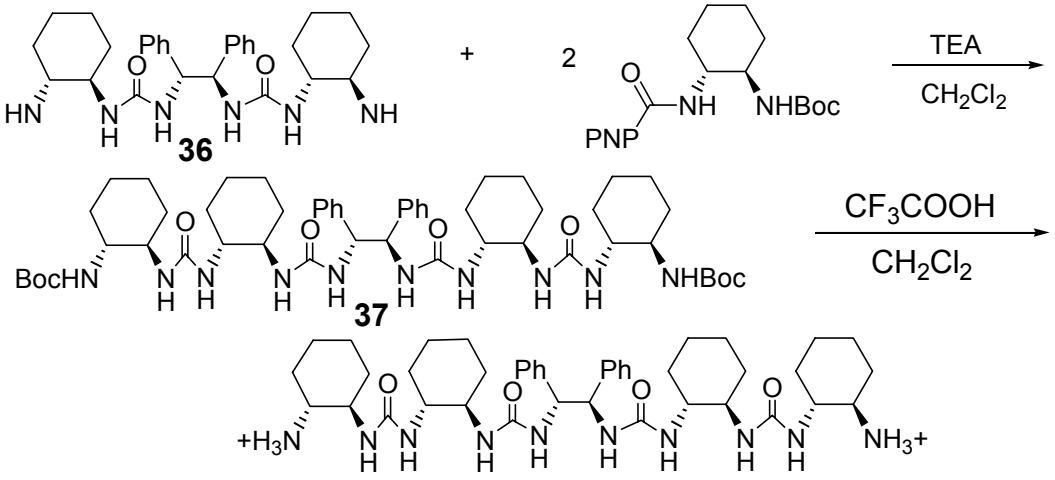


Figure 4.39 Synthesis of pentaurea 37

Following procedure **4.5.21** (synthesis of compound **35**), compound **37** was obtained as a colorless solid and further purified by column (yield: 90%), and the deprotected form was obtained as a salt by following procedure **4.5.6** (yield: 100%). Crystals of the deprotected form of compound **37** were grown in EtOH.

Compound **37**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.16-7.11 (m, 6H), 7.06-7.04 (m, 4H), 6.55-6.54 (m, 4H), 5.92 (d, 2H), 5.87 (d, 2H, *J* = 5.6 Hz), 5.72 (d, 2H, *J* = 8.0Hz), 4.89 (d, 2H), 3.35-3.00 (m, 8H), 2.00-1.53 (m, 16H), 1.35 (s, 18H), 1.17-1.03 (m, 16H); ^{13}C NMR (DMSO-*d6*) δ 158.6, 157.5, 155.5, 141.5, 127.7, 127.4, 126.6, 77.4, 58.5, 55.0, 53.5, 52.3, 32.6, 32.3, 28.3, 24.6, 24.3; MALDI (MNa^{+}) 995; IR (KBr) 3445 (s), 2934 (m), 2856 (w), 1684 (m), 1638 (s), 1578 (m), 1533 (m); decomp. 248 °C.

Deprotected form of compound **37**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.61 (br, 6H), 7.15-7.10 (m, 6H), 6.95-6.94 (m, 4H), 6.56 (d, 2H), 5.99 (d, 2H, *J* = 8.0 Hz), 5.96 (d, 2H, *J* = 6.8 Hz), 5.71 (d, 2H), 4.81 (d, 2H, *J* = 6.4 Hz), 3.36 (m, 2H), 3.25 (m, 2H), 2.98 (m, 2H), 2.90 (m, 2H), 1.77 (m, 8H), 1.54 (br, 8H), 1.40-0.80 (m, 16H); ^{13}C NMR (DMSO-*d6*) δ 158.0, 157.7, 141.1, 127.6, 127.5, 126.7, 58.6, 54.4, 53.8, 52.2, 50.7, 32.8, 32.1, 31.5, 29.4, 24.5, 24.4, 24.2, 23.3; MALDI (MNa^{+}) 795; IR (KBr) 3366 (m), 2937 (m), 2862 (w), 1653 (s), 1559 (s), 1203 (s), 1134 (m); decomp.195 °C.

4.5.23 Synthesis of all R heptaurea $(DACH)_3$-DPEDA-$(DACH)_3$ (38)

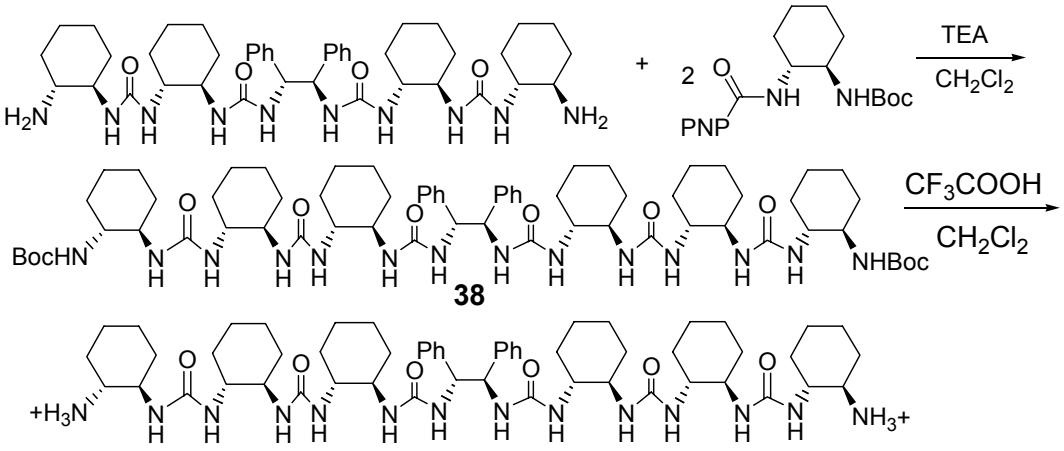


Figure 4.40 Synthesis of all R heptaurea 38

Following procedure **4.5.21**, compound **38** was obtained as a colorless solid and further purified by column (yield: 90%) and the deprotected form was obtained as a salt by following procedure **4.4.6** (yield: 100%).

Compound **38**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.13 (br, 6H), 7.12 (br, 4H), 6.55 (br, 4H), 6.00-5.68 (br, 10H), 4.86 (br, 2H), 3.52-3.14 (m, br, 10H), 2.96 (m, 2H), 1.98-1.42 (m, br, 24H), 1.23 (s, 18H), 1.19-1.07 (m, br, 24H); IR (KBr) 3338 (s), 2931 (s), 2856 (m), 1685 (m), 1640 (s), 1561 (s); decomp. 220 °C.

Deprotected form of compound **38**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.74 (br, 6H), 7.14 (m, 6H), 7.01(m, 4H), 6.54 (d, 2H), 6.02 (d, 2H, J = 8.4 Hz), 5.95 (d, 2H), 5.92 (d, 2H), 5.84 (d, 2H), 5.72 (d, 2H, J = 7.2 Hz), 4.87 (d, 2H), 3.50-3.00 (m, 10H), 2.68 (m, 2H), 2.00-1.50 (br, m, 24H), 1.40-0.90 (br, m, 24H); ^{13}C NMR (DMSO-*d6*) δ 154.7, 154.5, 153.9, 137.7, 124.1, 123.8, 123.0, 54.9, 50.9, 50.3, 49.6, 48.8, 48.6, 47.5, 28.9 (br), 28.8 (br), 28.2, 20.8 (br), 20.6 (br), 19.8; MALDI (MNa^+) 1075.7; IR (KBr) 3427 (s), 2935 (m), 2858 (w), 1638 (s), 1560 (m), 1204 (w), 1137 (w); decomp. 200 °C.

4.5.24 Synthesis of Boc-DPEDA-PNP (39)

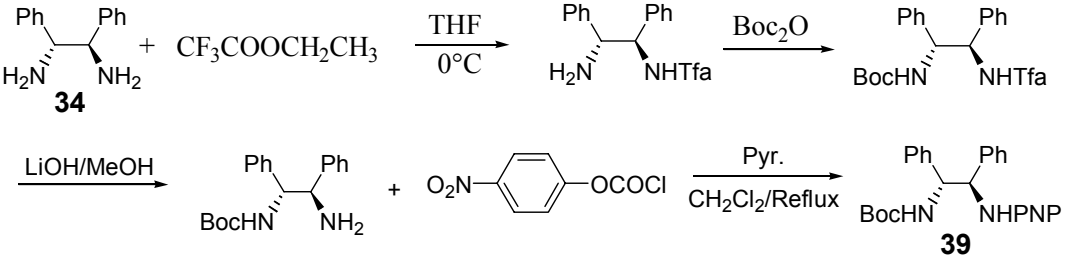


Figure 4.41 Synthesis of Boc-DPEDA-Tfa

To a cooled solution of **34** (1.06 g, 5 mmol) in CH_2Cl_2 (50 mL) was added CF_3COOEt (0.7 g, 5 mmol). The reaction mixture was stirred overnight at room temperature. Mono Tfa-DPEDA was recovered by removing the solvent and ethanol (yield: 100%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.21 (br, 1H), 7.21-7.11 (m, 10H), 4.92 (d, 2H, J = 8.0 Hz), 4.21 (d, 1H, J = 8.0 Hz).

To a cooled solution of Mono Tfa-DPEDA (1.52 g, 5 mmol) in CH_2Cl_2 (50 mL) was added Boc_2O (1.2 g, 5.3 mmol). The reaction mixture was stirred overnight at room temperature. 20 mL water was added, and the organic layer was separated and dried with Na_2SO_4. Tfa-DPEDA-Boc (1.95 g) was recovered by removing the solvent (yield: 98%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.78 (d, 1H, J = 9.2Hz), 7.65 (d, 1H, J = 9.6 Hz), 7.24-7.11 (m, 10H), 5.23 (dd, 1H), 5.07 (dd, 1H), 1.25 (s, 9H).

Tfa-DPEDA-Boc (1.95 g, 5 mmol) was refluxed for 2h in 15 mL LiOH (200 mg, 8.36 mmol) in MeOH with 10% distilled water, and then evaporated under reduced pressure. The

residue was then dissolved with heating in EtOAc (20 mL) and distilled water (5 mL), The aqueous layer was removed and the organic layer was dried with Na_2SO_4 and then EtOAc was removed under reduced pressure to give Mono Boc-DPEDA 1.33 g (yield: 85%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.350 (d, 1H), 7.211-7.127 (m, 10H), 4.620 (dd, 1H), 4.008 (d, 1H, *J* = 6.8 Hz), 1.302 (s, 9H).

Following procedure **4.5.1**, Boc-DPEDA-PNP **39** was obtained in 97% yield.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.59 (d, 1H), 8.18 (m, 2H), 7.50 (d, 1H), 7.31-7.15 (m, 12H), 5.03 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 156.0, 152.7, 144.1, 128.0, 127.0, 126.9, 126.2, 125.2, 122.1, 115.8, 78.1, 59.7, 58.4, 28.1; IR (KBr) 3438 (s), 1720 (m), 1683 (m), 1522 (m), 1490 (m), 1218 (m); mp 152-155 °C.

4.5.25 Synthesis of all R triurea DPEDA-DACH-DPEDA (40)

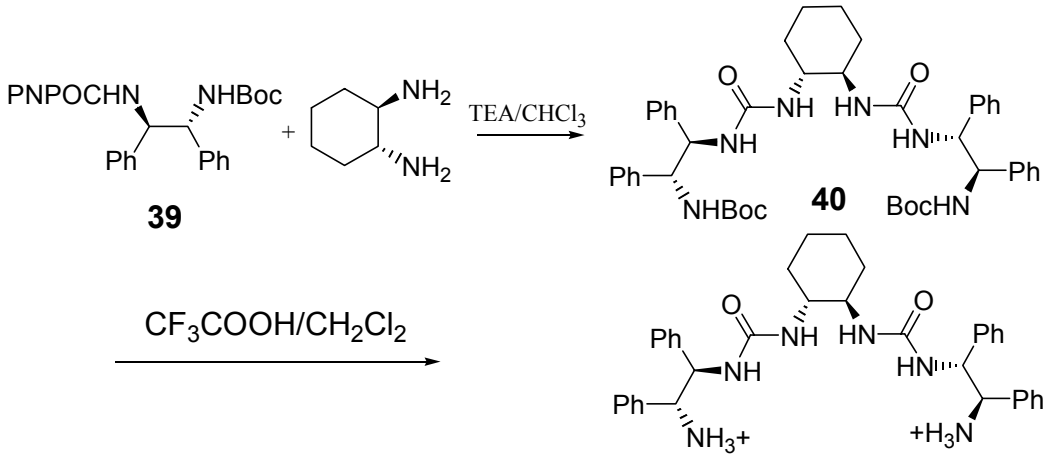


Figure 4.42 Synthesis of triurea DPEDA-DACH-DPEDA

Following procedure **4.5.2**, compounds **1** and **39** were reacted to give **40** in 94% yield. The deprotected form was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Compound **40**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.40 (d, 2H), 7.05-7.40 (m, 20H), 6.62 (d, 2H), 5.74 (d, 2H), 4.94 (t, 2H), 4.78 (t, 2H), 3.15 (m, 2H), 1.78 (d, 2H), 1.55 (d, 2H), 1.28 (s, 18H), 0.95-1.20 (m, 4H); MALDI (MNa^+) m/z 813.

Deprotected form of compound **40**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.27-6.95 (m, 20H), 5.10 (d, 2H), 4.40 (d, 2H), 3.40 (br, 2H), 2.04 (br, 2H), 1.74 (br, 2H), 1.33 (m, 4H); ^{13}C NMR (400 MHz, CD_3OD) δ 160.4, 142.4, 139.4, 135.9, 130.4, 130.1, 129.9, 129.8, 129.4, 129.2, 129.2, 128.8, 127.8, 67.6, 61.6, 59.5, 55.0, 34.0, 25.9; MALDI (MNa^+) 614; IR (KBr) 3415 (s), 3035 (w), 2935 (m), 1676 (s), 1559 (m), 1204 (s), 1137 (m); mp 160-163 °C.

4.5.26 Synthesis of RSR triurea DACH-DPEDA-DACH (41)

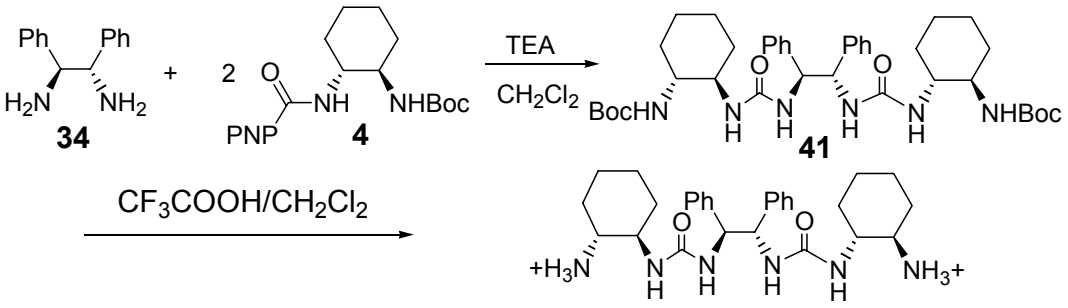


Figure 4.43 Synthesis of RSR triurea 41

Compound **4** (200 mg, 0.53 mmol) was added to a solution of **34** (S) (50 mg, 0.24 mmol) and TEA (100 μL, 0.72 mmol) in CH_2Cl_2 (10 mL), the reaction mixture was stirred and refluxed overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with dilute aq. NaOH, water and brine. After drying (Na_2SO_4) and filtering, the solvent was removed under reduced pressure to give the colorless product 145 mg (yield: 89%).

Compound **41**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.17 (m, 6H), 6.95-6.93 (m, 4H), 6.62 (d, 2H, *J* = 7.6 Hz), 6.26 (d, 2H, *J* = 6.8 Hz), 5.91 (d, 2H, *J* = 7.2 Hz), 4.95 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 157.4, 155.5, 140.4, 127.7, 127.5, 126.6, 77.5, 57.4, 53.8, 52.2, 32.7, 32.1, 28.3, 24.2; MALDI (MNa^+) 692; IR (KBr) 3412 (s), 3034 (w), 2942 (m), 1654 (s), 1561 (s), 1204 (s), 1136 (m); mp 145-148 °C.

Deprotected form of compound **41**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.80 (s, 6H), 7.24-7.16 (m, 6H), 7.04-7.02 (m, 4H), 6.62 (d, 2H, *J* = 8 Hz), 6.32 (d, 2H, *J* = 7.6 Hz), 4.98 (d, 2H, *J* = 8.0 Hz), 3.34 (m, 2H), 2.85-2.79 (m, 2H), 1.96-1.93 (m, br, 2H), 1.70-1.64 (m, br, 6H), 1.40-1.14 (m, br, 8H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 157.9, 140.2, 127.7, 127.6, 126.9, 58.3, 54.4, 51.3, 31.3, 2 9.3, 24.0, 23.1; MALDI (MNa^+) 492; IR (KBr) 3423 (s), 2943 (m), 1649 (s), 1561 (m), 1203 (s), 1138 (m); mp 185-190 °C.

4.5.27 Synthesis of SRSRS pentaurea (42)

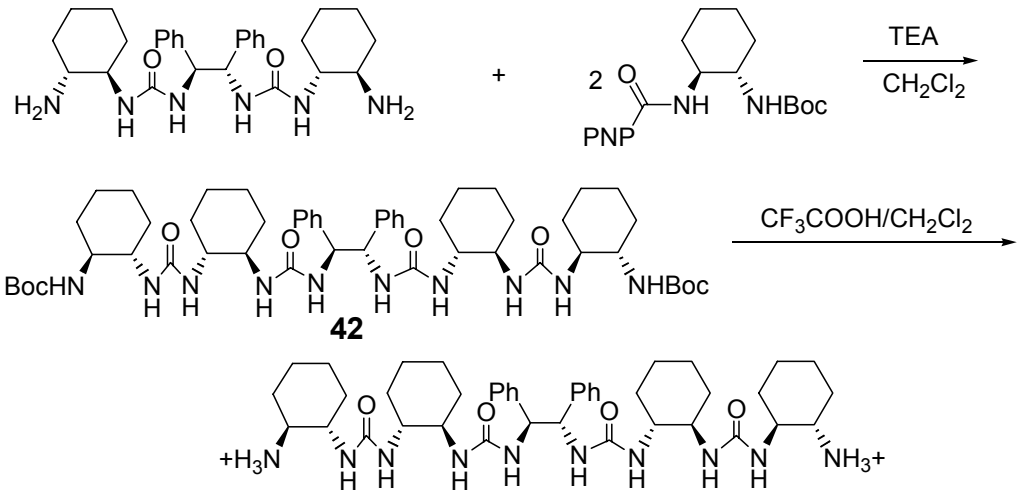


Figure 4.44 Synthesis of alternate RS pentaurea based on DACH and DPEDA

Following procedure **4.5.26,** compound **42** was obtained as a colorless solid and further purified by column (yield: 90%). The deprotected form was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Compound **42**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.13-7.13 (m, 6H), 6.95 (d, 4H, *J* = 6.4 Hz), 6.59 (d, 2H, *J* = 7.6 Hz), 6.33 (d, 2H), 6.09 (d, 2H, *J* = 6.4 Hz), 5.93 (d, 2H, *J* = 6.4 Hz), 5.80 (d, 2H, *J* = 6.0 Hz), 4.89 (d, 2H, *J* = 6.8 Hz), 3.34-3.14 (m, 8H), 1.85-1.49 (m, 16H), 1.37 (s, 18H), 1.23-1.05 (m, 16H); ^{13}C NMR (DMSO-*d6*) δ 158.0, 157.4, 155.4, 140.8, 127.6, 126.6, 77.5, 58.0, 53.8, 52.5, 48.6, 37.4, 32.5, 28.3, 24.3, 24.2; IR (KBr) 3388(s), 2933 (s), 2858 (m), 1644 (s), 1556 (s), 1169 (m); mp 192-196 °C.

Deprotected form of compound **42**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.76 (s, 6H), 7.18-7.17 (m, 6H), 7.00-6.98 (d, 4H), 6.55 (br, 2H), 6.17-5.95 (m, 6H), 4.87 (d, 2H), 3.30 (br, 6H), 2.82 (m, 2H), 1.93-1.55 (m, 16H), 1.35-1.21 (m, 16H); ^{13}C NMR (DMSO-*d6*) δ 158.4, 157.8, 140.4, 127.7, 127.6, 126.8, 60.2, 54.8, 54.5, 51.5, 51.3, 31.4, 29.5, 29.4, 24.1, 23.7, 23.3; MALDI (MNa^{+}) 795; IR (KBr) 3369 (s), 2939 (s), 2862 (m), 1765 (s), 1562 (s), 1203 (s), 1137 (s); decomp. 176 °C.

4.5.28 Synthesis of alternate RS heptaurea (43)

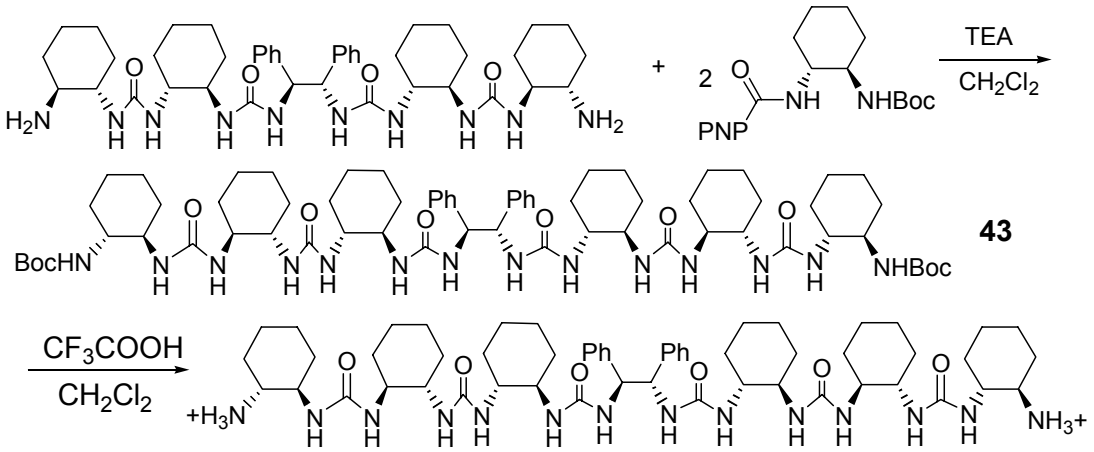


Figure 4.45 Synthesis of alternate RS heptaurea 43

Following procedure **4.5.26,** compound **43** was obtained as a colorless solid and further purified by column (yield: 83%). The deprotected form was obtained as a salt by following procedure **4.5.6 (**yield: 100%).

Compound **43**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.14 (br, 6H), 6.96 (br, 4H), 6.75-5.75 (m, 14H), 4.88 (br, 2H), 3.40-3.00 (br, 12H), 1.80 (br, 12H), 1.54 (br, 12H), 1.36 (s, 18H), 1.30-1.00 (br, 24H); ^{13}C NMR (DMSO-*d6*) δ 158.7, 158.5, 158.2, 156.1, 128.2, 127.2, 79.8, 56.7, 54.4, 53.1 (m), 33.2 (m), 28.9, 25.1, 24.9, 24.3, 19.2; IR (KBr) 3381 (s), 2933 (s), 2858 (m), 1644 (s), 1557 (s), 1451 (m); mp 178-182 °C.

Deprotected form of compound **43**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.83 (s, 6H), 7.21 (m, 6H), 6.95 (d, 4H), 6.44 (br, 2H), 6.24 (br, 6H), 5.97 (br, 2H), 4.91 (d, 2H), 3.40-3.18 (m, 10H), 2.80 (br, 2H), 2.00-1.42 (m, 24H), 1.40-1.04 (m, 24H); ^{13}C NMR (DMSO-*d6*) δ 158.6, 158.0, 157.6, 139.8, 127.8, 126.9, 58.0 (br), 54.6 (br), 52.4 (br), 51.5, 31.5 (br), 29.5, 23.6 (br), 24.2, 23.4; MALDI (MNa^{+}) 1076; IR (KBr) 3413 (s), 2935 (m), 2860 (w), 1637 (s), 1569 (s), 1203 (m), 1138 (m); decomp.198-205 °C.

4.5.29 Synthesis of RRSRR pentaurea (44)

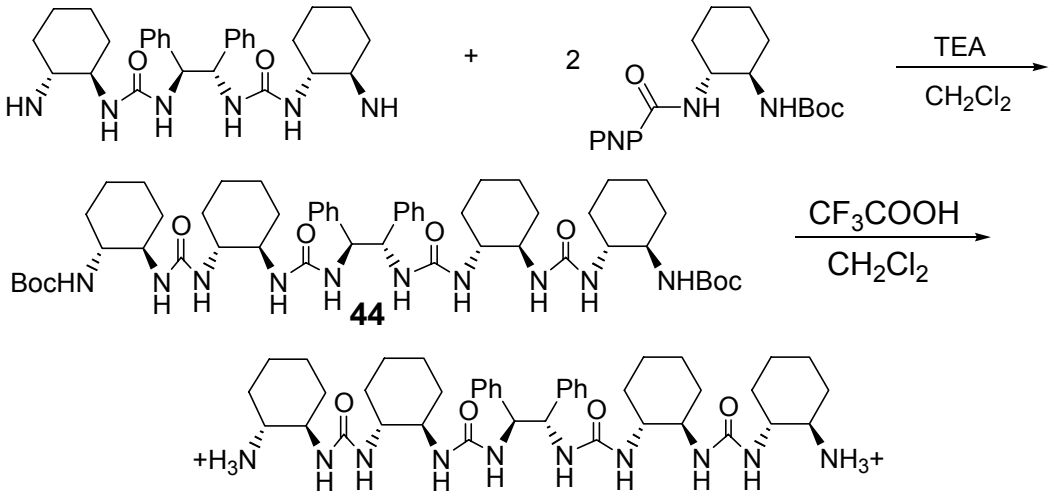


Figure 4.46 Synthesis of RRSRR pentaurea 44

Following procedure **4.5.26,** compound **44** was obtained as a colorless solid and further purified by column (yield: 86%). The deprotected form was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Compound **44**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.16 (br, 6H), 6.95 (br, 4H), 6.58 (d, 2H), 6.38 (br, 2H), 6.04 (d, 2H), 5.92 (br, 4H), 4.93 (d, 2H), 3.40 (m, 2H), 3.24 (m, 2H), 3.18 (m, 2H), 3.08 (m, 2H), 1.98-1.42 (m, 16H), 1.352 (s, 18H), 1.30-1.00 (m, 16H); ^{13}C NMR (DMSO-*d6*) δ 158.5, 157.2, 155.4, 127.6, 127.5, 126.6, 77.4, 57.7, 55.4, 52.2 (br), 32.6, 32.4, 28.2, 24.6, 24.3, 23.9 (br); IR (KBr) 3411 (s), 2933 (m), 2857 (m), 1686 (s), 1638 (s), 1561 (s), 1173 (m); decomp. 221 °C.

Deprotected form of compound **44**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.78 (s, 6H), 7.21 (m, 6H), 6.88 (br, 4H), 6.30 (br, 2H), 6.10 (m, 6H), 5.00 (d, 2H), 3.46 (m, 2H), 3.38 (m, 2H), 3.20 (m, 2H), 2.80 (m, 2H), 2.0-1.42 (m, 16H), 1.40-1.00 (m, 16H); ^{13}C NMR (DMSO-*d6*) δ 158.1, 157.5, 139.5, 127.8, 127.5, 126.8, 57.6, 54.6, 31.7, 29.5, 24.3, 23.9, 23.4; MALDI (MNa^{+}) 795; IR (KBr) 3408 (s), 2940 (m), 2863 (w), 1647 (s), 1560 (s), 1204 (s), 1140 (m); mp 186-188 °C.

4.5.30 Synthesis of RRRSRRR heptaurea (45)

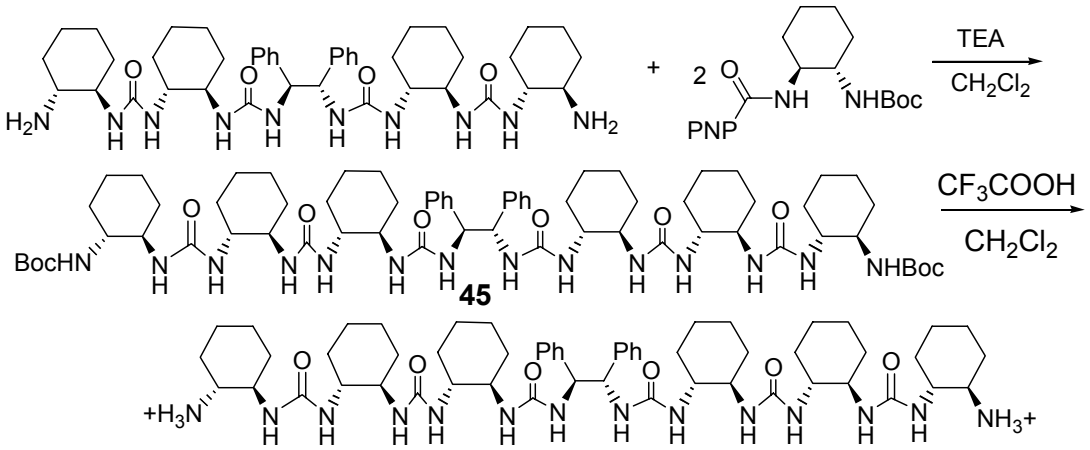


Figure 4.47 Synthesis of RRRSRRR heptaurea 45

Following procedure **4.5.26,** compound **45** was obtained as a colorless solid and further purified by column (yield: 75%). The deprotected form was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Compound **45**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.18 (br, 6H), 7.00 (m, 4H), 6.57 (d, 2H), 6.10-5.70 (m, 12H), 4.90 (d, 2H), 3.40-2.96 (m, 12H), 2.0-1.7 (br, 12H), 1.7-1.45 (br, 12H), 1.40 (s, 18H), 1.34-1.00 (br, 24H); ^{13}C NMR was not obtained because of its poor solubility; MALDI (MNa^{+}) 1276; IR (KBr) 3414 (s), 2932 (m), 2856 (w), 1637 (s), 1560 (m); decomp. 215 °C.

Deprotected form of compound **45**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.73 (s, 6H), 7.14 (br, 6H), 6.92 (br, 4H), 6.24 (br, 2H), 6.06-6.00 (m, 10H), 4.90 (d, 2H), 3.40-3.00 (10H), 2.66 (m, 2H), 1.96-1.40 (m, 12H), 1.40-0.96 (m, 12H); ^{13}C NMR (DMSO-*d6*) δ 158.2, 158.1, 157.2, 140.3, 127.6, 127.5, 126.6, 59.7, 57.6 (br), 54.4, 54.3 (br), 52.4 (br), 51.1, 32.5 (br), 31.9, 29.5, 24.4 (br), 24.2, 24.0 (br), 23.3; MALDI (MNa^{+}) 1076; IR (KBr) 3430 (s), 2938 (m), 1638 (m), 1560 (m), 1204 (m), 1140 (m); mp 178-181 °C.

4.5.31 Synthesis of triurea DACH-EDA-DACH (46)

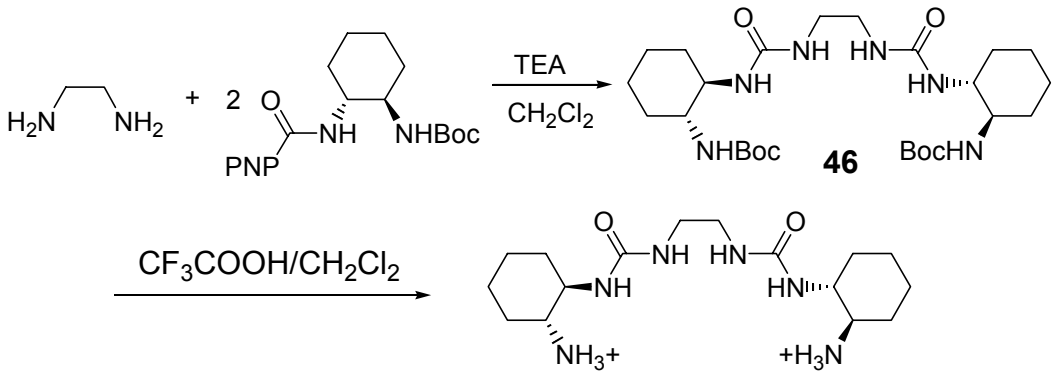


Figure 4.48 Synthesis of triurea DACH-EDA-DACH

Following procedure **4.5.26,** compound **46** was obtained as a colorless solid and further purified by column (yield: 95%). The deprotected form was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Compound **46**: ^{1}H NMR (DMSO-*d6*) δ 6.54 (d, 2H), 5.95 (d, 2H), 5.68 (d, 2H), 3.20 (m, 2H), 3.00 (m, 2H), 2.90 (br, 4H), 1.77 (br, 4H), 1.55 (br, 4H), 1.32 (s, 18H), 1.20-1.00 (m, 8H); ^{13}C NMR was not obtained because of the poor solubility of this compound; IR (KBr) 3341 (s), 2977 (w), 2938 (m), 2854 (w), 1684 (s), 1637 (s), 1562 (s), 1526 (s), 1320 (m), 1278 (m), 1172 (m); mp 243-245 °C.

Deprotected form of compound **46**: ^{1}H NMR (DMSO-*d6*) δ 7.76 (br, 6H), 6.19 (d, 2H), 6.14 (br, 2H), 3.38 (m, 2H), 3.13 (m, 2H), 3.00 (m, 2H), 2.74 (m, 2H), 1.93-1.63 (m, 8H), 1.33-1.12 (m, 8H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.4, 54.6, 51.1, 31.8, 29.5, 24.3, 23.4; MALDI (MNa^{+}) 363; IR (KBr) 3415 (s), 2943 (m), 1677 (s), 1205 (m), 1138 (m); decomp. the compound changed color at around 190 °C, and became a black liquid at around 200 °C.

4.5.32 Synthesis of pentaurea (DACH)$_2$-EDA-(DACH)$_2$ (47)

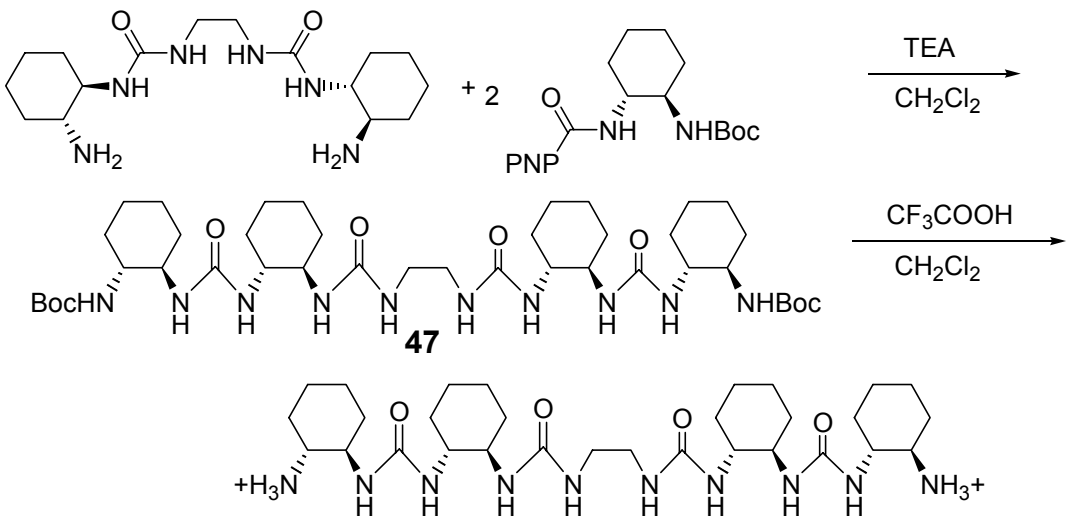


Figure 4.49 Synthesis of pentaurea $(DACH)_2$-EDA-$(DACH)_2$

Following procedure **4.5.26,** compound **47** was obtained as a colorless solid and further purified by column (yield: 90%). The deprotected form was obtained as a salt by following procedure **4.5.6** (yield: 100%).

Compound **47**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.51 (d, 2H), 5.91 (br, 2H), 5.82 (br, 6H), 3.29-3.16 (m, 12H), 1.79 (m, 8H), 1.55 (m, 8H), 1.31 (s, 18H), 1.21-0.96 (m, 16H); ^{13}C NMR was mot obtained because of its poor solubility; IR (KBr) 3426 (s), 2933 (w), 2856 (w), 1685 (m), 1637 (s), 1581 (m), 1530 (m); decomp. 240 °C.

Deprotected form of compound **47**: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.79 (br, 6H), 6.04 (m, 4H), 5.96 (d, 2H), 5.88 (d, 2H), 3.42 (m, 2H), 3.36 (m, 2H), 3.12 (m, 2H), 2.96 (m, 4H), 2.75 (m, 2H), 1.96-1.55 (m, 16H), 1.40-1.16 (m, 16H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 158.3, 158.2, 59.8, 54.5, 53.9, 52.6, 51.0, 32.7, 32.2, 31.8, 29.5, 24.4, 24.3, 23.4, 20.8; MALDI (MNa^{+}) 643; IR (KBr) 3378 (s), 2940 (m), 2864 (w), 1676 (s), 1653 (s), 1569 (s), 1204 (s), 1140 (m); mp 180-185 °C.

4.5.33 Synthesis of triurea (48)

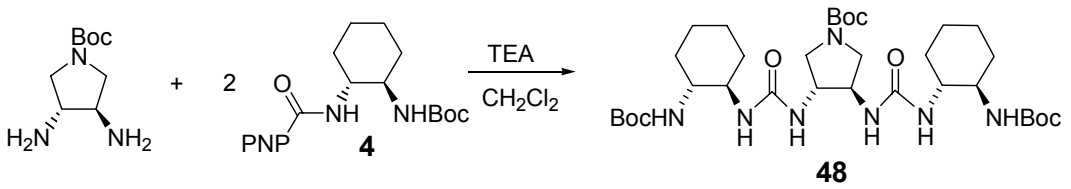


Figure 4.50 Synthesis of compound 48

Compound **4** (350 mg, 0.92 mmol) was added to a solution of diamine (80 mg, 0.4 mmol) and TEA (100 μL, 0.72 mmol) in CH_2Cl_2 (5 mL), the reaction mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (80 mL) and washed with dilute aq. NaOH, water and brine. After drying (Na_2SO_4) and filtering, the solvent was removed under reduced pressure to give the colorless product 240 mg (yield: 88%).

^{1}H NMR (400MHz, DMSO-*d6*) δ 6.56 (t, 2H, *J* = 8.0 Hz), 6.30 (d, 2H, *J* = 5.2 Hz), 5.75 (br, 2H), 3.78 (br, 2H), 3.48 (m, 2H), 3.28 (m, 2H), 3.06 (m, 2H), 2.94 (m, 2H), 1.78 (br, 4H), 1.59 (br, 4H), 1.38 (s, 9H), 1.35 (s, 18H), 1.19-1.00 (m, 8H) ; ^{13}C NMR (DMSO-*d6*) δ 157.8, 157.7, 155.5, 153.4, 78.3, 77.4, 77.3, 54.3, 54.2, 53.9, 53.0, 52.7, 50.4, 49.7, 32.8, 32.1, 28.2, 28.1, 24.5, 24.4; IR (KBr) 3414 (s), 2936 (w), 1684 (s), 1640 (s); decomp. 236-239 °C.

4.5.34 Synthesis of Boc-(DACH)$_{SS}$-NBDAP-(DACH)$_{SS}$-Boc (49)

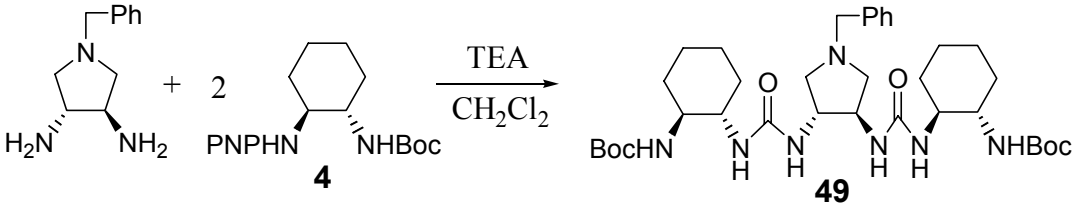


Figure 4.51 Synthesis of compound 49

Compound **4** (S) (320 mg, 0.84 mmol) was added to a solution of 3,4-diaminopyrrolidine (74 mg, 0.39 mmol) and TEA (100 μL, 0.72 mmol) in CH_2Cl_2 (5 mL), the reaction mixture was refluxed overnight. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with dilute aq. NaOH, water and brine. After drying (Na_2SO_4) and filtering, the solvent was removed under reduced pressure to give the colorless product 245 mg (yield: 94%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.30-7.23 (m, 5H), 6.52 (d, 2H, *J* = 8 Hz), 6.24 (d, 2H, *J* = 5.6 Hz), 5.75 (br, 2H), 3.71 (m, 2H), 3.49 (s, 2H), 3.26 (br, 2H), 3.04 (m, 2H), 2.75 (m, 2H), 2.17 (br, 2H), 1.78 (br, 4H), 1.58 (br, 4H), 1.31 (s, 18H), 1.30-1.00 (m, 8H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 157.9, 155.4, 128.5, 128.1, 126.9, 77.3, 59.5, 54.6, 52.3, 34.9, 32.7, 32.2, 28.2, 24.5, 24.3; IR (KBr) 3414 (s), 2937 (w), 1685 (m), 1637 (m); decomp. the compound changed color at around 185 °C, and became a black liquid at around 220 °C.

4.5.35 Synthesis of Boc-DACH-DATHF-DACH-Boc (50)

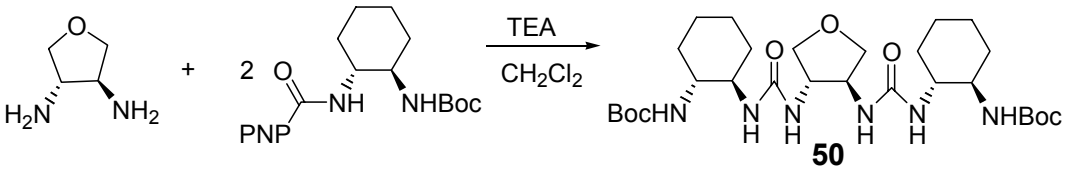


Figure 4.52 Synthesis of compound 50

Following procedure **4.5.33**, compound **50** was obtained as a colorless solid (yield: 97%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.54 (d, 2H, *J* = 8 Hz), 6.33 (d, 2H, *J* = 5.2 Hz), 5.83 (br, 2H), 3.84 (m, 2H), 3.78 (br, 2H), 3.40 (d, 2H, *J* = 6 Hz), 3.28 (m, 2H), 3.07 (br, 2H), 1.80 (m, 4H), 1.59 (br, 4H), 1.35 (s, 18H), 1.16 (br, 8H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 157.9, 155.4, 77.4, 71.9, 56.1, 54.5, 52.5, 32.7, 32.2, 28.2, 24.5, 24.3; IR (KBr) 3334 (s), 2930 (m), 2855 (w), 1684 (s), 1639 (s), 1567 (m), 1534 (m); decomp.180 °C.

4.5.36 Synthesis of Boc-$(DPEDA)_{R,R}$-$(DACH)_{S,S}$-$(DAP)_{R,R}$-$(DACH)_{S,S}$-$(DPEDA)_{R,R}$-Boc (51)

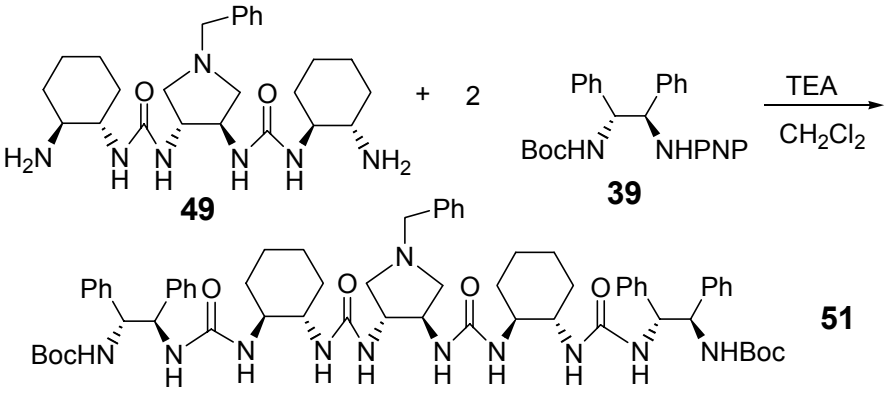


Figure 4.53 Synthesis of compound 51

Compound **49** (75 mg, 0.11 mmol, protected) was refluxed in CF_3COOH /CH_2Cl_2 overnight, then the solvent was removed and the product was dried under high vacuum. The product was reacted with **39** (120 mg, 0.26 mmol), TEA (200 μL) in 20 mL CH_2Cl_2 overnight. 70 mg of product was recovered (yield: 57%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.31-7.08 (m, 27H), 6.70 (d, 2H, *J* = 8.8 Hz), 6.10 (d, 2H, *J* = 6 Hz), 5.86 (br, 2H), 5.72 (d, 2H, *J* = 7.2 Hz), 4.95 (t, 2H, *J* = 7.2 Hz, 8.8 Hz), 4.81 (t, 2H, *J* = 8.8 Hz, 7.2 Hz), 3.71 (d, 2H), 3.45 (q, 2H, *J* = 13.2 Hz), 3.23 (m, 2H), 3.07 (m, 2H), 2.75 (m, 2H), 2.15 (m, 2H), 1.78 (br, 4H), 1.55 (br, 4H), 1.26 (s, 18H), 1.19-0.93 (m, 8H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 157.9, 157.4, 155.0, 141.3, 141.2, 138.6, 128.4, 128.1, 127.7, 127.1, 127.0, 126.9, 126.5, 77.8, 57.7, 28.1; IR (KBr) 3441 (s), 2932 (w), 1686 (m), 1647 (s), 1560 (m);

decomp. the compound changed color at around 200 °C, and became a black liquid at around 222 °C.

4.5.37 Synthesis of bis-activated DACH (52)

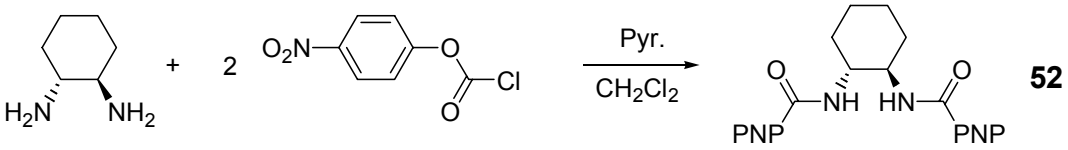


Figure 4.54 Synthesis of bis-activated DACH

4-Nitrophenyl chloroformate (1.14 g, 5.68 mmol) was dissolved in CH_2Cl_2 (5 mL), (1*R*,2*R*)-(+)-*trans*-1,2-diaminocyclohexane (0.32 g, 2.81 mmol) was dissolved in a mixture of dry CH_2Cl_2 (5 mL) and pyridine (453 µL, 0.44 g, 5.68 mmol), the resulting mixture was added to the first solution, and the solution was refluxed for 6 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with 1M $NaHCO_3$ solution, water and brine. The solvent was dried (Na_2SO_4) and removed under reduced pressure to yield the colorless product 1.0 g (yield: 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (4H, m), 7.25 (4H, m), 5.43 (2H, d), 3.55 (2H, m), 2.19 (2H, d), 1.86 (2H, m), 1.37 (4H, d); ^{13}C NMR (DMSO-*d6*) δ 24.3, 31.5, 54.2, 122.0, 125.2, 143.9, 152.2, 156.3; MALDI (MNa^+) 467; IR (KBr):3306 (s), 3080 (w), 2941 (m), 2921 (m), 2859 (m), 1707 (s), 1614, 1595 (m), 1544, 1349 (s), 1237 (s), 857 (m); mp 154-157 °C.

4.5.38 Synthesis of cyclized DACH triurea (53)

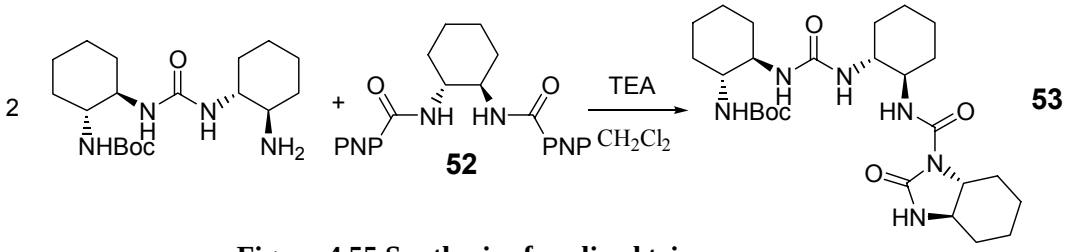


Figure 4.55 Synthesis of cyclized triurea

Bis-activated diamine **52** (0.15 g, 0.34 mmol) was added to a solution of mono-Boc-protected diurea (0.21 g, 0.60 mmol) and TEA (100 µL, 0.73 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at RT until **52** was consumed (as evidenced by TLC). The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with dilute aq. NaOH, water and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure to give the colorless product. Crystals of the deprotected form of **53** were grown in CH_3CN/H_2O.

^{1}H NMR (400 MHz, DMSO-*d6)* δ 7.90 (d, 1H), 7.59 (s,1H), 6.55 (d, 1H), 5.90 (d, 1H), 5.70 (d, 1H), 3.25 (m, 4H), 2.95 (m, 4H), 2.65 (d, 2H),1.81-1.34 (m, 20H), 1.35 (s, 9H), 1.25-1.00 (m, 20H); ^{13}C NMR was not obtained because of the poor solubility; MALDI (MNa^+) 543; IR (KBr) 3333 (s), 2933 (s), 2857 (m), 1722 (s), 1688 (s), 1644 (s), 1557 (s), 1449 (s), 1365 (m), 1320 (m), 1278 (m), 1252 (m), 1175 (m); decomp. 215 °C.

4.5.39 Synthesis of cyclized triurea DACH$_2$-DPEDA (55)

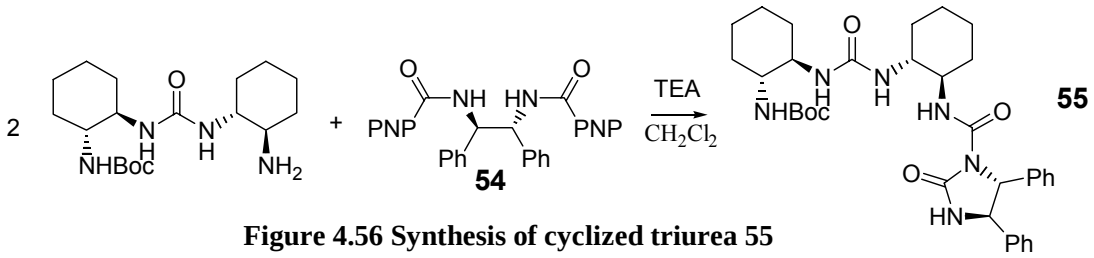


Figure 4.56 Synthesis of cyclized triurea 55

Following procedure **4.5.38**, compound **55** was obtained as a colorless solid (yield: 97%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.36 (s, 1H), 8.26 (d, 1H), 7.32 (m, 10H), 6.60 (d, 1H), 5.85 (d, 1H), 5.62 (d, 1H), 4.91 (d, 1H), 4.39 (d, 1H), 1.35 (s, 9H); ^{13}C NMR (DMSO-*d6*) δ 158.3, 157.4, 152.1, 141.7, 128.9, 128.7, 128.1, 127.6, 125.7, 125.3, 77.4, 65.0, 60.4, 59.7, 55.1, 53.3, 52.2, 51.4, 32.5 (m), 28.2, 24.1 (m); MALDI (MNa^+) 641; IR (KBr) 3311 (s), 2933 (s), 2857 (m), 1730 (s), 1547 (s); mp 223 °C.

4.5.40 Synthesis of RS DACH diurea (58)

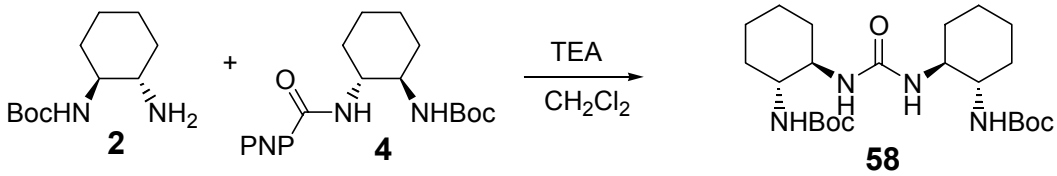


Figure 4.57 Synthesis of RS diurea

Compound **4** (S) (120 mg, 0.32 mmol) was added to a solution of **2** (56 mg, 0.26 mmol) and TEA (100 µL, 0.72 mmol) in $_{CH2Cl2}$ (5 mL), the reaction mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with dilute aq. NaOH, water and brine. After drying (Na_2SO_4) and filtering, the solvent was removed under reduced pressure to give the colorless product 115 mg (yield: 97%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.56 (d, 2H, *J* = 7.6 Hz), 5.81 (d, 2H, *J* = 8.0 Hz)), 3.25 (m, 2H), 3.02 (m, 2H), 1.81 (br, 4H), 1.58 (br, 4H), 1.35 (s, 18H), 1.19-1.00 (br, 8H); ^{13}C NMR (DMSO-*d6*) δ 158.1, 155.4, 77.4, 53.5, 52.4, 32.5, 32.0, 28.3, 24.2; IR (KBr) 3434 (s), 2936 (m), 1680 (s), 1632 (s), 1521 (s), 1320 (m), 1180 (m); mp 220-221 °C.

4.5.41 Synthesis of thiourea dimer (59)

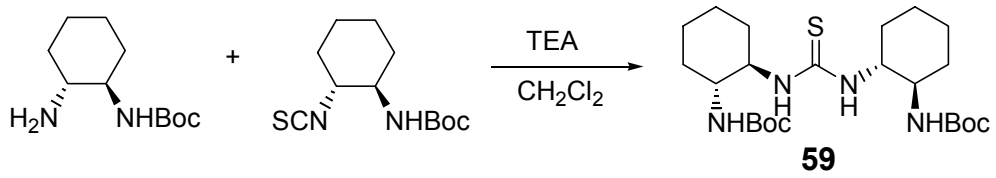


Figure 4.58 Synthesis of thiourea dimer

To a solution of **2** (450 mg, 2.1 mmol) in CH_2Cl_2 (50 mL) was added the isothiocyanate (540 mg, 2.1 mmol). The solution was stirred 2 days at room temperature. The CH_2Cl_2 was removed in vacuo. The solid was purified by flash chromatography to give 0.7 g of a white solid (71%). Crystals were grown in EtOAc.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.23 (d, 2H, *J* = 7.6 Hz), 6.70 (d, 2H, *J* = 7.2 Hz), 3.94 (br, 2H), 3.22 (m, 2H), 2.00 (br, 2H), 1.79 (br, 2H), 1.61 (br, 4H), 1.36 (s, 18H), 1.30-1.00 (m, 8H) ; ^{13}C NMR (DMSO-*d6*) δ 180.0, 155.7, 77.8, 56.7, 53.6, 32.1, 31.8, 28.2, 24.3, 24.17; IR (KBr) 3380 (s), 3264 (s), 2978 (m), 2936 (m), 2855 (m), 1692 (s), 1566 (s), 1519 (s), 1367 (s), 1172 (s); mp 218-220 °C.

4.5.42 Synthesis of thiourea trimer (60)

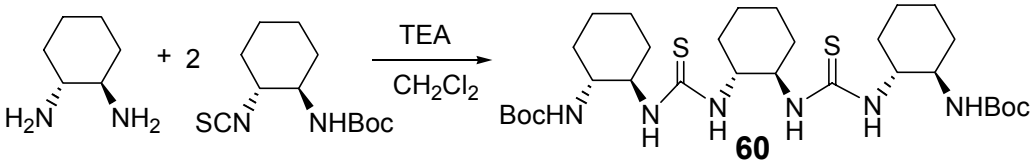


Figure 4.59 Synthesis of thiourea trimer

Following procedure **4.5.41**, compound **60** was obtained as a white solid in 74% yield.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.48 (d, 2H, *J* = 5.6 Hz), 7.20 (d, 2H, *J* = 6.0 Hz), 6.69 (d, 2H, *J* = 7.6 Hz), 4.01 (m, 2H), 3.93 (m, 2H), 3.20 (m, 2H), 2.05 (br, 4H), 1.78 (br, 2H), 1.61 (br, 6H), 1.36 (s, 18H), 1.20-1.08 (br, 12H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 155.7, 77.7, 57.1, 53.6, 32.0, 31.9, 24.3, 24.2; IR (KBr) 3446 (s), 2934 (m), 2855 (m), 1692 (s), 1547 (s), 1521 (s), 1366 (m), 1171 (m); MALDI (MH^+) 627; mp 200-204 °C.

4.5.43 Synthesis of pseudopentaurea (61)

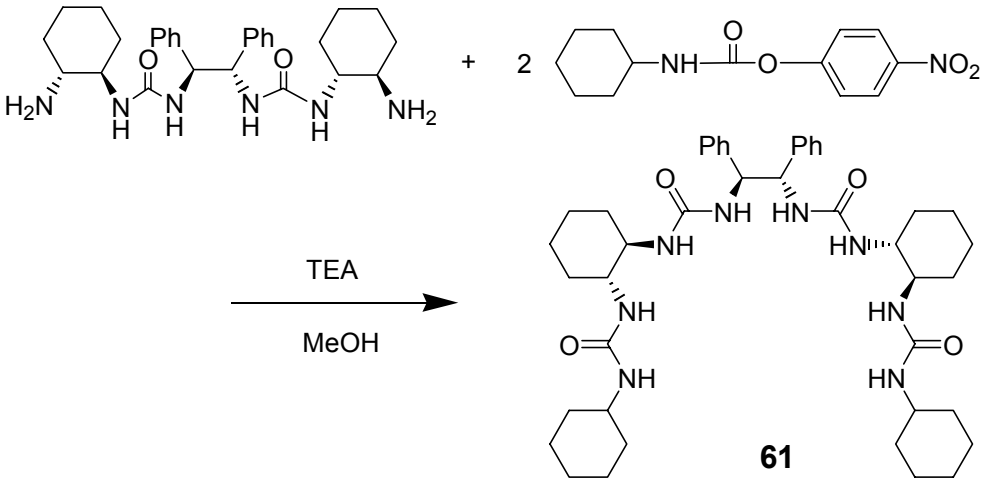


Figure 4.60 Synthesis of pseudopentaurea 61

Following procedure **4.5.41**, compound **61** was obtained as a white solid in 90% yield, crystals were grown in MeOH (No NMR data were obtained, but the crystal structure was determined).

4.6 Crystals growth

Single crystals suitable for X-ray diffraction study were obtained for 12 compounds, among them 11 were grown by slow evaporation, the other one was grown by slow cooling. Initially, a supersaturated solution of a compound was prepared in a clean vial, the vial was capped by parafilm or a plastic cap poked with holes. The vial was then left to sit in a quiet place for a couple of days or even a week until the crystals were obtained.

Table 4.1 Crystal growth conditions

Compound	Sovlent	Method
5	MeOH/EtOAc	Slow evaporation
6	MeOH/EtOAc	Slow evaporation
12	MeOH/H_2O	Slow evaporation
13	MeOH	Slow evaporation
27	MeOH	Slow evaporation
35	MeOH	Slow evaporation
36	MeOH	Slow evaporation
37	EtOH	Slow evaporation
41(deprotected	MeOH	Slow evaporation

form)		
53	CH_3CN/H_2O	Slow cooling
59	EtOAc	Slow evaporation
61	MeOH	Slow evaporation

4.7 Purification of oligoureas by HPLC

Prep. reverse-phase HPLC was used to further purify the oligoureas for the CD study. The complete kit includes a C18 column, a Waters™ 490E programmable multiwavelength detector, a Waters™ 600 controller, a Waters™ 600 pump, and a PreLC™ 25mm module. Eluent was mixtures of either CH_3CN and water or MeOH and water depending on the solubility of the compound; flow rate was between 10 ml/min. to 15 mL/min.; UV detection was at 230nm, 245nm, 255nm, and 265nm, the retention time was chain length dependent, the longer the chain, the longer the retention time.

4.8 CD experiments

CD spectra were recorded by using JASCO-810 spectrometer. The quartz cell had 1 mm path length, measurements were carried out at 1.0 nm resolution and a scan rate of 200 nm/min, wavelength was between 185 and 230 nm, and data were averaged for 20 scans. Also data were normalized for oligourea concentration and (if necessary) the number of residues. Concentrations of solutions were around 0.2 mmol. Aggregation was not detected by dilution studies.

4.9 Solubility determination by UV-Vis

UV-Vis adsorption was used to measure the solubility of all-R and alternate-RS- DACH heptaureas. The experiments were run on a Shimadzu UV-3101PC UV-Vis-NIR scanning spectrophotometer. The general procedure is described with alternate-RS- DACH heptaurea as an example: a bulk solution of known concentration was prepared by dissolving 18 mg of the compound in 25 mL of water; a saturated solution of the same compound was prepared. The solution of the known concentration was diluted to 1/2, 1/3, 1/4, 1/5 respectively to prepare a calibration curve (plotting with MS excel) against which to determine the concentration of the saturated solution. The saturated solution was diluted so te absorbance signal was on the dynamic range of detection of the spectrophotometer. The point of saturation was obtained by back calculating the concentration of the saturated solution.

4.10 Conclusions

Both chiral C_2-symmetric 1,2-diamines and one achiral 1,2-diamine were chosen as the building blocks for the target C_2-symmetric oligoureas. Except for the achiral monomer, all chiral diamines were synthesized in the lab.

Syntheses of homochiral (all monomers have the same absolute configuration) and heterochiral (not all monomers have the same absolute configuration) oligoureas based on the same monomer and different monomers were accomplished in solution phase, growing a chain by adding one unit at a time in one direction or two units at a time in two directions with PNP activated Boc protected diamines as the intermediates. All the chiral oligoureas were purified by either recrystallization or column chromatography/HPLC and characterized by NMR and MS. For some oligoureas, crystal structures were obtained.

Fragment condensation was attempted to improve the efficiency of the syntheses, but it led to cyclized oligoureas instead of the desired chain molecules.

Some thioureas were also synthesized, crystal structure was obtained for a thiourea dimer.

4.11 References

(1) Larrow, J. F., Jacobsen, E. N. *J. Org. Chem*. **1994**, *59*, 1939.

(2) Pikul, S.; Corey, E. J. *Organic Syntheses*, Vol 71, 1993.

(3) Skarzewski, J.; Gupta, A. *Tetrahedron: Asym.* **1997**, *8*, 1861.

(4) Nielsen, P. E. *Chem. Eur*. *J*. **1997**, *3*, 912.

(5) Xu, D., Prasad, K., Repic, O., Blacklock, T. J. *Tetrahedron Lett*. **1995**, *36*, 7357.

(6) Tye, H.; Eldred, C.; Wills, M. *Tetrahedron Lett.* **2002**, *43*, 155.

(7) Weygand, F.; Swodenk, W. *Chem. Ber*. **1957**, *90*, 639.

(8) Burgess, K. *Solid-Phase organic synthesis*; John Wiley & Sons: New York, 2000.

(9) Wang, S. S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.

(10) Jochims, J. C.; Seeliger, A. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 174.

(11) Smith, J.; Liras, J. L.; Schneider, S. E.; Anslyn, E. V. *J. Org. Chem.* **1996**, *61*, 8811.

Appendices

A.1 Crystal data and structure refinement for **5**, **12**, and **13**

Compound	**5**	**12**	**13**
Empirical formula	$C_{23}\ H_{42}\ N_4\ O_5$	$C_{90}\ H_{166}\ N_{18}\ O_{20}$	$C_{26}\ H_{50}\ F_6\ N_6\ O_9$
Formula weight	454.61	1820.41	704.72
Temperature (K)	88.5(2)	90.0(2)	90.0(2)
Wavelength (Å)	0.71073	1.54178	0.71073
Crystal system, Space group	Orthorhombic, P 212121	Monoclinic, P 21	Orthorhombic, P 21 21 2
Unit cell dimensions			
a (Å)	9.9750(3)	14.9839(5)	18.502(4)
b (Å)	11.4910(3)	21.4941(8)	9.7200(19)
c (Å)	22.1460(6)	16.6980(7)	9.910(2)
α (°)	90	90	90
β (°)	90	107.014(2)	90
γ (°)	90	90	90
V ($Å^3$)	2538.44(12)	5142.5(3)	1782.2(6)
Z,Calculated Density (Mg/m^3)	4, 1.190	2, 1.176	2, 1.313
Absorption Coefficient	0.084	0.676	0.118

(mm^{-1})			
F(000)	992	1984	748
Crystal size (mm)	0.35 x 0.25 x 0.20	0.12 x 0.12 x 0.08	0.30 x 0.30 x 0.15
θ range for data collection	1.84 to 27.48 deg.	2.77 to 67.98	2.20 to 27.46 deg.
Limiting indices	-12<=h<=12, -14<=k<=14, -28<=l<=28	-17<=h<=17, -25<=k<=25, 0<=l<=20	-23<=h<=22, -12<=k<=12, -11<=l<=12
Reflections collected / unique	21634 / 5804 [R(int) = 0.0651]	18205 / 18205 [R(int) = 0.0772]	12305 / 4074 [R(int) = 0.0345]
Completeness to theta =	(27.48) 99.9 %	(67.98) 98.6 %	(27.46) 99.9 %

Absorption correction	None	Semi-empirical from equivalents	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints /parameters	5804 / 0 / 295	18205 / 1087 / 1172	4074 / 0 / 215
Goodness-of-fit on F^2	1.038	1.023	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0526, wR2 = 0.0956	R1 = 0.0590, wR2 = 0.1630	R1 = 0.0589, wR2 = 0.1587
R indices (all data)	R1 = 0.0696, wR2 = 0.1007	R1 = 0.0636, wR2 = 0.1684	R1 = 0.0795, wR2 = 0.1719
Absolute structure parameter	-0.9(9)	0.11(5)	0.2(12) i.e. undefined.
Extinction coefficient			
Largest diff. peak and hole (e $Å^{-3}$)	.259 and -.234	.680 and -.344	

A. 2 Crystal data and structure refinement for **27**, **35**, and **36**

Compound	**27**	**35**	**36**
Empirical formula	C_{25} H_{44} F_6 N_6 O_7	C_{38} H_{56} N_6 O_6	C_{32} H_{42} F_6 N_6 O_6
Formula weight	654.66	692.89	720.72
Temperature (K)	90.0(2)	90.0(2)	90.0(2)
Wavelength (Å)	0.71073	0.71073	1.54178
Crystal system, Space group	Monoclinic, P 21	Orthorhombic, P 212121	Monoclinic, P 21
Unit cell dimensions			
a (Å)	11.3124(2)	5.1332(3	11.4109(4)
b (Å)	13.9297(2)	21.8171(14)	16.1539(5)
c (Å)	20.1360(3)	33.141(2)	11.5562(4)
α (°)	90	90	90
β (°)	91.2812(6)	90	106.863(2)
γ (°)	90	90	90
V ($Å^3$)	3172.20(9)	3711.5(4)	2038.57(12)
Z, Calculated Density (Mg/m^3)	4, 1.371	4, 1.240	2, 1.174
Absorption Coefficient (mm^{-1})	0.122	0.085	0.859
F(000)	1384	1496	756

Crystal size (mm)	0.30 x 0.20 x 0.15	0.50 x 0.07 x 0.08	0.15 x 0.13 x 0.02
θ range for data collection	1.01 to 25.00 deg	1.12 to 22.50 deg.	4.00 to 67.91 deg.
Limiting indices	-13<=h<=13, -16<=k<=16, -23<=l<=23	-5<=h<=5, -23<=k<=23, -35<=l<=35	-13<=h<=13, -18<=k<=19, -13<=l<=13
Reflections collected / unique	22343 / 11187 [R(int) = 0.0411]	18655 / 2871 [R(int) = 0.1699]	24738 / 24738 [R(int) = 0.0533]
Completeness to theta =	(25.00) 100.0 %	(22.50) 100.0 %	(67.91) 99.2 %

Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	11187 / 412 / 871	2871 / 745 / 457	24738 / 151 / 556
Goodness-of-fit on F^2	1.030	1.198	1.121
Final R indices [I>2sigma(I)]	R1 = 0.0627, wR2 = 0.1503	R1 = 0.0737, wR2 = 0.1451	R1 = 0.0606, wR2 = 0.1732
R indices (all data)	R1 = 0.0866, wR2 = 0.1632	R1 = 0.0977, wR2 = 0.1527	R1 = 0.0684, wR2 = 0.1837
Absolute structure parameter	0.1(9) i.e. indeterminate		-0.02(5)
Extinction coefficient			
Largest diff. peak and hole (e $Å^{-3}$)	.736 and -.334	.352 and -.243	.260 and -.240

A.3 Crystal data and structure refinement for **37**, **41** (deprotected), and **53**

Compound	**37**	**41** (deprotected)	**53**
Empirical formula	$C_{50}\ H_{83}\ F_6\ N_{10}\ O_{12.50}$	$C_{33.50}\ H_{44}\ F_6\ N_6\ O_{7.50}$	$C_{21}\ H_{38}\ N_6\ O_4$
Formula weight	1138.26	764.75	438.57
Temperature (K)	90.0(2)	90.0(2)	86.0(2)
Wavelength (Å)	1.54178	0.71073	0.71073
Crystal system, Space group	Orthorhombic, P 21 21 21	Triclinic, P 1	Orthorhombic, P 212121
Unit cell dimensions			
a (Å)	9.8175(3)	12.1674(2)	5.1510(10)
b (Å)	23.3594(7)	12.5553(2)	19.127(2)
c (Å)	25.2881(7)	14.2809(3)	22.281(2)
α (°)	90	89.3621(7)	90
β (°)	90	73.4955(8)	90
γ (°)	90	69.1252(8)	90
V ($Å^3$)	5799.3(3)	1944.53(6)	2195.2(5)
Z, Calculated Density (Mg/m^3)	4, 1.393	2, 1.306	4, 1.327
Absorption Coefficient (mm^{-1})	0.918	0.111	0.093

F(000)	2616	802	952
Crystal size (mm)	0.15 x 0.15 x 0.10	0.35 x 0.22 x 0.10	0.32 x 0.26 x 0.02
θ range for data collection	2.57 to 68.02 deg.	1.49 to 25.00 deg.	1.40 to 23.99 deg.
Limiting indices	-11<=h<=10, -28<=k<=28, -30<=l<=29	-14<=h<=14, -14<=k<=14, -16<=l<=16	-5<=h<=5, 0<=k<=21, 0<=l<=25
Reflections collected / unique	65833 / 10421 [R(int) = 0.0481]	13661 / 13661 [R(int) = 0.0000]	3425 / 3425 [R(int) = 0.0000]
Completeness to theta =	(68.02) 99.1 %	(25.00) 100.0 %	(23.99) 100.0 %

Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	None
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2

Data / restraints / parameters	10421 / 711 / 790	13661 / 15 / 985	3425 / 7 / 298
Goodness-of-fit on F^2	1.082	1.058	1.147
Final R indices [I>2sigma(I)]	R1 = 0.0668, wR2 = 0.1779	R1 = 0.0633, wR2 = 0.1487	R1 = 0.0702, wR2 = 0.0954
R indices (all data)	R1 = 0.0695, wR2 = 0.1801	R1 = 0.1020, wR2 = 0.1678	R1 = 0.0903, wR2 = 0.0998
Absolute structure parameter	0.09(4)	-0.6(7) i.e. undetermined	
Extinction coefficient	0.00180(15)		0.0044(9)
Largest diff. peak and hole (e $Å^{-3}$)	.736 and -.297	.678 and -.465	.207 and -.182

A.4 Crystal data and structure refinement for **59** and **61**

Compound	**59**	**61**
Empirical formula	C_{23} H_{42} N_4 O_4 S	C42 H62 N8 O5
Formula weight	470.67	759.00
Temperature (K)	90.0(2)	90.0(2)
Wavelength (Å)	0.71073	1.54178
Crystal system, Space group	Triclinic, P 1	Trigonal, P 31 2 1
Unit cell dimensions		
a (Å)	5.2101(2)	16.701(2)
b (Å)	11.1110(5)	16.701(2)
c (Å)	23.1870(13)	14.783(3)
α (°)	88.704(2)	90
β (°)	87.939(2)	90
γ (°)	89.590(2)	120
V ($Å^3$)	1341.04(11)	3571.0(10)
Z, Calculated Density (Mg/m^3)	2, 1.166	3, 1.059
Absorption Coefficient (mm^{-1})	0.154	0.565
F(000)	512	1230

Crystal size (mm)	0.22 x 0.15 x 0.12	0.12 x 0.10 x 0.10
θ range for data collection	1.76 to 25.00 deg.	3.06 to 68.07 deg.
Limiting indices	-6<=h<=6, -13<=k<=13, -27<=l<=27	-19<=h<=20, -20<=k<=20, -15<=l<=17
Reflections collected / unique	8953 / 8953 [R(int) = 0.0000]	47113 / 4331 [R(int) = 0.0545]
Completeness to theta =	(25.00) 98.9 %	(68.07) 99.9 %
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2

Data / restraints / parameters	8953 / 81 / 601	4331 / 148 / 264
Goodness-of-fit on	1.082	1.055

F^2		
Final R indices [I>2sigma(I)]	R1 = 0.0723, wR2 = 0.1192	R1 = 0.0479, wR2 = 0.1259
R indices (all data)	R1 = 0.1217, wR2 = 0.1334	R1 = 0.0502, wR2 = 0.1276
Absolute structure parameter	0.08(11)	0.16(6)
Extinction coefficient		
Largest diff. peak and hole (e $Å^{-3}$)	.386 and -.252	.225 and -.234

A.5 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **5**

	x	y	z	U(eq)
O(1)	9031(1)	7457(1)	9989(1)	21(1)
O(2)	4939(1)	6147(1)	8660(1)	26(1)
O(3)	6538(1)	4864(1)	8974(1)	22(1)
O(4)	4988(1)	8618(1)	11357(1)	23(1)
O(5)	6510(1)	10095(1)	11290(1)	20(1)
N(1)	7057(2)	8175(1)	9622(1)	21(1)
N(2)	7148(1)	6602(1)	8640(1)	19(1)
N(3)	7062(1)	7004(1)	10458(1)	20(1)
N(4)	7198(1)	8334(1)	11542(1)	18(1)
C(1)	7799(2)	7537(1)	10020(1)	17(1)
C(2)	7602(2)	8536(2)	9042(1)	19(1)
C(3)	7419(2)	9840(2)	8936(1)	25(1)
C(4)	7972(2)	10209(2)	8323(1)	31(1)
C(5)	7344(2)	9507(2)	7813(1)	28(1)
C(6)	7536(2)	8206(2)	7916(1)	22(1)
C(7)	6970(2)	7837(1)	8528(1)	18(1)
C(8)	6107(2)	5895(2)	8754(1)	18(1)
C(9)	5564(2)	3952(2)	9135(1)	23(1)
C(10)	4623(2)	4388(2)	9627(1)	26(1)
C(11)	6450(2)	2992(2)	9382(1)	33(1)
C(12)	4831(2)	3541(2)	8572(1)	30(1)
C(13)	7692(2)	6522(1)	10996(1)	17(1)
C(14)	7578(2)	5197(2)	11028(1)	22(1)

C(15)	8298(2)	4726(2)	11581(1)	25(1)
C(16)	7766(2)	5281(2)	12159(1)	25(1)
C(17)	7853(2)	6608(2)	12127(1)	21(1)
C(18)	7125(2)	7071(1)	11571(1)	16(1)
C(19)	6134(2)	8983(2)	11389(1)	17(1)
C(20)	5502(2)	10969(2)	11113(1)	19(1)
C(21)	4483(2)	11127(2)	11620(1)	24(1)
C(22)	6330(2)	12071(2)	11056(1)	30(1)
C(23)	4894(2)	10634(2)	10508(1)	24(1)

A.6 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **12**.

	x	y	z	U(eq)
O(1A)	858(2)	-1375(1)	3875(2)	40(1)
O(2A)	1968(1)	-642(1)	3944(1)	28(1)
C(2A)	1175(2)	-785(1)	3903(2)	25(1)
N(3A)	475(2)	-379(1)	3855(2)	27(1)
C(4A)	649(2)	290(1)	3940(2)	24(1)
C(5A)	-30(2)	647(1)	3228(2)	29(1)
C(6A)	170(2)	1344(1)	3307(2)	39(1)
C(7A)	117(3)	1582(1)	4154(2)	44(1)
C(8A)	772(2)	1222(1)	4878(2)	39(1)
C(9A)	594(2)	524(1)	4800(2)	30(1)
N(10A)	1243(2)	174(1)	5474(2)	34(1)
O(11A)	120(1)	-182(1)	6024(1)	35(1)
C(11A)	924(2)	-195(1)	5988(2)	29(1)
N(12A)	1584(2)	-580(1)	6486(2)	37(1)
C(13A)	1350(2)	-1044(1)	7016(2)	31(1)
C(14A)	1593(2)	-1697(2)	6761(2)	38(1)
C(15A)	1364(2)	-2207(2)	7305(2)	42(1)
C(16A)	1861(2)	-2081(2)	8228(2)	41(1)
C(17A)	1618(2)	-1445(1)	8492(2)	35(1)
C(18A)	1822(2)	-922(1)	7949(2)	29(1)
N(19A)	1557(2)	-327(1)	8214(2)	33(1)
C(20A)	2155(2)	175(1)	8378(2)	29(1)
O(20A)	2947(1)	139(1)	8314(1)	34(1)
N(21A)	1786(2)	701(1)	8599(2)	33(1)
C(22A)	2388(2)	1226(1)	8960(2)	31(1)

C(23A)	2147(2)	1809(1)	8411(2)	36(1)
C(24A)	2800(2)	2345(2)	8798(2)	43(1)
C(25A)	2771(2)	2485(1)	9688(2)	39(1)
C(26A)	3000(2)	1903(1)	10239(2)	30(1)
C(27A)	2354(2)	1364(1)	9849(2)	25(1)
N(28A)	2584(2)	808(1)	10367(2)	28(1)
O(29A)	1127(1)	654(1)	10475(1)	27(1)
C(29A)	1920(2)	469(1)	10559(2)	24(1)
O(30A)	2244(1)	-94(1)	10858(1)	29(1)
C(31A)	1610(2)	-558(1)	11054(2)	24(1)
C(32A)	775(2)	-674(1)	10292(2)	28(1)
C(33A)	2219(2)	-1138(1)	11251(2)	35(1)
C(34A)	1340(2)	-349(1)	11818(2)	26(1)
C(35A)	1499(2)	-1900(1)	3882(2)	36(1)
C(36A)	1811(2)	-1882(1)	3099(2)	34(1)
C(37A)	878(3)	-2464(2)	3851(4)	68(1)
C(38A)	2314(3)	-1894(2)	4684(2)	48(1)
O(1B)	4168(1)	-1293(1)	3728(2)	37(1)
O(2B)	5244(1)	-527(1)	3848(1)	28(1)
C(2B)	4453(2)	-694(1)	3770(2)	26(1)
N(3B)	3719(2)	-313(1)	3683(2)	26(1)
C(4B)	3869(2)	354(1)	3817(2)	24(1)
C(5B)	3179(2)	730(1)	3118(2)	27(1)
C(6B)	3365(2)	1426(1)	3243(2)	33(1)
C(7B)	3313(2)	1633(1)	4101(2)	36(1)
C(8B)	3969(2)	1256(1)	4803(2)	33(1)
C(9B)	3791(2)	556(1)	4680(2)	28(1)
N(10B)	4426(2)	188(1)	5325(2)	30(1)
O(11B)	3345(1)	-131(1)	5963(1)	31(1)
C(11B)	4128(2)	-182(1)	5863(2)	26(1)
N(12B)	4767(2)	-615(1)	6261(2)	34(1)

C(13B)	4665(2)	-976(1)	6958(2)	26(1)
C(14B)	4838(2)	-1669(1)	6822(2)	34(1)
C(15B)	4754(2)	-2076(2)	7547(2)	42(1)
C(16B)	5419(2)	-1847(2)	8375(2)	42(1)
C(17B)	5238(2)	-1168(2)	8519(2)	39(1)
C(18B)	5328(2)	-757(1)	7793(2)	30(1)
N(19B)	5151(2)	-105(1)	7902(2)	45(1)
O(20B)	6639(1)	161(1)	8610(1)	34(1)
C(20B)	5815(2)	302(1)	8316(2)	34(1)
N(21B)	5518(2)	901(1)	8315(2)	45(1)
C(22B)	6012(2)	1348(1)	8945(2)	31(1)
C(23B)	5884(2)	1997(1)	8550(2)	39(1)
C(24B)	6359(2)	2488(1)	9169(2)	35(1)
C(25B)	6011(2)	2487(1)	9945(2)	38(1)
C(26B)	6166(2)	1850(1)	10353(2)	37(1)
C(27B)	5683(2)	1342(1)	9737(2)	31(1)
N(28B)	5842(2)	728(1)	10100(2)	39(1)
O(29B)	4431(1)	623(1)	10327(1)	32(1)
C(29B)	5194(2)	414(1)	10350(2)	31(1)
O(30B)	5508(1)	-154(1)	10632(2)	36(1)
C(31B)	4903(2)	-597(1)	10902(2)	26(1)
C(32B)	4028(2)	-724(1)	10179(2)	29(1)
C(33B)	5505(2)	-1180(1)	11085(2)	36(1)
C(34B)	4693(2)	-361(1)	11685(2)	31(1)
C(35B)	4867(2)	-1796(1)	3860(2)	35(1)
C(36B)	5316(2)	-1789(1)	3146(2)	36(1)
C(37B)	4280(3)	-2376(2)	3787(3)	52(1)
C(38B)	5572(2)	-1743(2)	4717(2)	40(1)
O(1C)	7694(1)	-1226(1)	4308(2)	35(1)
O(2C)	8622(1)	-479(1)	4015(1)	30(1)
C(2C)	7899(2)	-637(1)	4141(2)	31(1)

N(3C)	7190(2)	-259(1)	4155(2)	38(1)
C(4C)	7260(2)	408(1)	4100(2)	32(1)
C(5C)	6689(2)	664(1)	3235(2)	32(1)
C(6C)	6789(2)	1370(1)	3204(2)	34(1)
C(7C)	6481(2)	1675(1)	3899(2)	39(1)
C(8C)	6992(2)	1425(1)	4760(2)	41(1)
C(9C)	6931(2)	714(1)	4802(2)	33(1)
N(10C)	7449(2)	513(1)	5631(2)	41(1)
O(11C)	6448(1)	-228(1)	5792(1)	34(1)
C(11C)	7231(2)	-21(1)	5985(2)	31(1)
N(12C)	7943(2)	-258(1)	6610(2)	38(1)
C(13C)	7859(2)	-819(1)	7059(2)	27(1)
C(14C)	8015(2)	-1408(2)	6617(2)	38(1)
C(15C)	7916(2)	-1995(1)	7102(2)	41(1)
C(16C)	8581(2)	-1966(1)	7987(2)	36(1)
C(17C)	8443(2)	-1375(1)	8440(2)	29(1)
C(18C)	8536(2)	-789(1)	7945(2)	23(1)
N(19C)	8388(2)	-242(1)	8392(2)	29(1)
O(20C)	9723(1)	266(1)	8365(1)	30(1)
C(20C)	8955(2)	264(1)	8513(2)	22(1)
N(21C)	8616(2)	769(1)	8825(2)	27(1)
C(22C)	9209(2)	1287(1)	9210(2)	24(1)
C(23C)	8996(2)	1880(1)	8688(2)	27(1)
C(24C)	9640(2)	2415(1)	9117(2)	29(1)
C(25C)	9548(2)	2532(1)	9994(2)	29(1)
C(26C)	9753(2)	1940(1)	10519(2)	26(1)
C(27C)	9117(2)	1406(1)	10093(2)	24(1)
N(28C)	9319(2)	847(1)	10606(2)	26(1)
O(29C)	7812(1)	633(1)	10514(1)	26(1)
C(29C)	8630(2)	478(1)	10706(2)	23(1)
O(30C)	8977(1)	-66(1)	11064(1)	28(1)

C(31C)	8344(2)	-554(1)	11195(2)	26(1)
C(32C)	7666(2)	-749(1)	10368(2)	31(1)
C(33C)	9013(2)	-1080(1)	11578(2)	37(1)
C(34C)	7868(2)	-330(1)	11830(2)	28(1)
C(35C)	8330(2)	-1744(1)	4261(2)	35(1)
C(36C)	8414(2)	-1796(2)	3378(2)	39(1)
C(37C)	7832(2)	-2306(1)	4475(2)	44(1)
C(38C)	9269(2)	-1658(2)	4928(2)	36(1)
O(2W)	9415(2)	815(1)	6643(2)	49(1)

A.7 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **13**

	x	y	z	U(eq)
C(1)	2001(1)	4134(2)	11795(3)	19(1)
C(2)	2641(2)	4446(3)	12715(3)	24(1)
C(3)	2411(2)	4388(3)	14201(3)	26(1)
C(4)	2082(2)	2991(3)	14530(3)	31(1)
C(5)	1450(2)	2676(3)	13594(3)	29(1)
C(6)	1666(1)	2741(3)	12111(3)	20(1)
C(7)	1072(1)	1550(2)	10220(3)	20(1)
C(8)	366(1)	383(3)	8454(3)	23(1)
C(9)	436(2)	1250(4)	7187(3)	37(1)
C(10)	359(2)	388(5)	5913(3)	52(1)
N(1)	2243(1)	4172(2)	10356(2)	22(1)
N(2)	1043(1)	2467(2)	11259(2)	23(1)
N(3)	428(1)	1209(2)	9678(2)	24(1)
O(1)	1648(1)	1082(2)	9806(2)	29(1)
C(11)	-1353(2)	1709(3)	12425(3)	35(1)
C(12)	-1178(2)	2584(3)	11177(3)	27(1)
F(1)	-1986(2)	1060(3)	12358(2)	65(1)
F(2)	-865(2)	735(2)	12631(2)	68(1)
F(3)	-1369(1)	2482(2)	13544(2)	49(1)
O(2)	-1667(1)	2751(2)	10348(2)	39(1)
O(3)	-555(1)	3061(2)	11189(3)	44(1)
C(1S)	1315(3)	5429(4)	7398(4)	58(1)
O(1S)	1231(2)	4328(3)	8271(3)	54(1)
O(1W)	0	5000	9572(4)	54(1)

A.8 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **27**

	x	y	z	U(eq)
O(1A)	4014(3)	10459(2)	-1018(1)	27(1)
N(1A)	6929(3)	10786(3)	-513(2)	26(1)
C(1A)	7299(4)	10169(3)	-1084(2)	26(1)
O(2A)	3863(3)	7438(2)	1114(1)	26(1)
N(2A)	5410(3)	9307(3)	-1089(2)	25(1)
C(2A)	8174(4)	10720(3)	-1492(2)	32(1)
N(3A)	3596(3)	8949(3)	-668(2)	27(1)
C(3A)	8543(4)	10142(4)	-2097(2)	42(1)
N(4A)	3383(3)	8933(3)	730(2)	27(1)
C(4A)	7456(5)	9834(5)	-2508(2)	49(2)
N(5A)	5204(3)	8646(3)	1206(2)	27(1)
C(5A)	6590(4)	9278(4)	-2090(2)	39(1)
N(6A)	6435(3)	7181(3)	439(2)	27(1)
C(6A)	6211(4)	9861(3)	-1489(2)	24(1)
C(7A)	2473(4)	9169(3)	-370(2)	25(1)
C(8A)	1439(4)	8864(4)	-823(2)	31(1)
C(9A)	256(4)	9100(4)	-507(2)	31(1)
C(10A)	168(4)	8596(4)	166(2)	29(1)
C(11A)	1207(4)	8874(3)	622(2)	28(1)
C(12A)	2385(4)	8662(3)	310(2)	24(1)
C(13A)	6163(4)	8066(3)	1498(2)	24(1)
C(14A)	6810(4)	8635(3)	2045(2)	27(1)
C(15A)	7883(4)	8101(4)	2322(2)	34(1)
C(16A)	8743(4)	7821(4)	1773(2)	33(1)
C(17A)	8101(4)	7238(3)	1239(2)	29(1)

C(18A)	7038(4)	7776(3)	957(2)	23(1)
C(19A)	4312(4)	9616(3)	-932(2)	21(1)
C(20A)	4143(4)	8285(3)	1018(2)	22(1)
O(1B)	6031(3)	10879(2)	5918(2)	28(1)
N(1B)	3268(3)	11181(3)	5406(2)	24(1)
C(1B)	2831(4)	10558(3)	5943(2)	22(1)
O(2B)	6055(3)	7808(2)	3914(1)	26(1)
N(2B)	4711(3)	9668(2)	6037(2)	23(1)
C(2B)	1887(4)	11106(3)	6309(2)	26(1)
N(3B)	6522(3)	9363(3)	5603(2)	27(1)
C(3B)	1444(4)	10531(4)	6910(2)	34(1)
N(4B)	6561(3)	9343(3)	4200(2)	28(1)
C(4B)	2462(5)	10246(4)	7360(2)	42(1)
N(5B)	4721(3)	9003(3)	3771(2)	26(1)
C(5B)	3388(4)	9674(4)	6988(2)	33(1)
N(6B)	3439(3)	7632(3)	4568(2)	25(1)
C(6B)	3858(4)	10242(3)	6397(2)	23(1)
C(7B)	7601(4)	9614(3)	5266(2)	25(1)
C(8B)	8694(4)	9363(3)	5671(2)	29(1)
C(9B)	9824(4)	9608(4)	5306(2)	32(1)
C(10B)	9848(4)	9116(4)	4637(2)	37(1)
C(11B)	8749(4)	9358(4)	4225(2)	31(1)
C(12B)	7629(4)	9109(3)	4582(2)	25(1)
C(13B)	3795(4)	8400(3)	3474(2)	24(1)
C(14B)	3199(4)	8889(4)	2874(2)	32(1)
C(15B)	2196(4)	8290(4)	2584(2)	34(1)
C(16B)	1277(4)	8039(4)	3110(2)	36(1)
C(17B)	1865(4)	7537(3)	3697(2)	28(1)
C(18B)	2859(4)	8143(3)	3991(2)	23(1)
C(19B)	5771(4)	10002(3)	5857(2)	24(1)
C(20B)	5792(4)	8671(3)	3956(2)	21(1)

O(1C)	12376(3)	7876(3)	5767(2)	44(1)
O(2C)	10799(4)	6977(3)	5480(2)	49(1)
C(1C)	11466(5)	7404(4)	5882(3)	41(1)
C(2C)	11083(5)	7347(4)	6610(3)	45(1)
F(1C)	11916(4)	7666(4)	7061(2)	68(2)
F(2C)	10869(4)	6474(3)	6805(2)	48(1)
F(3C)	10144(5)	7901(4)	6707(2)	70(2)
F(1C')	10103(17)	6740(15)	6703(12)	91(7)
F(2C')	10797(19)	8131(11)	6845(12)	80(7)
F(3C')	11955(17)	6928(19)	6921(15)	138(11)
O(1D)	4414(4)	7 055(4)	-464(2)	24(1)
O(2D)	4782(5)	5467(4)	-523(3)	23(1)
C(1D)	4695(7)	6299(4)	-757(3)	26(1)
C(2D)	4970(6)	6346(4)	-1510(3)	29(1)
F(1D)	5100(4)	7233(2)	-1729(2)	37(1)
F(2D)	5926(3)	5853(3)	-1652(2)	44(1)
F(3D)	4078(4)	5931(3)	-1859(2)	44(1)
O(1D')	4730(20)	7104(16)	-438(10)	31(4)
O(2D')	4480(20)	5489(15)	-526(11)	24(3)
C(1D')	4570(30)	6328(13)	-741(6)	26(2)
C(2D')	4380(13)	6408(10)	-1509(7)	30(2)
F(1D')	4632(13)	7281(9)	-1725(9)	34(3)
F(2D')	5006(12)	5769(8)	-1827(6)	34(2)
F(3D')	3233(10)	6239(10)	-1659(7)	47(3)
O(1E)	5049(6)	5952(5)	5620(3)	26(2)
O(2E)	5282(14)	7546(6)	5563(3)	28(2)
C(1E)	5103(7)	6780(5)	5850(3)	27(1)
C(2E)	4862(6)	6805(5)	6593(3)	38(1)
F(1E)	4723(4)	7661(3)	6841(2)	44(1)
F(2E)	5632(4)	6294(3)	6945(2)	42(1)
F(3E)	3811(4)	6344(3)	6720(2)	62(1)

O(1E')	5290(30)	5950(20)	5629(14)	28(4)
O(2E')	5380(60)	7540(30)	5483(13)	26(4)
C(1E')	5290(30)	6801(19)	5817(6)	30(2)
C(2E')	5541(14)	6869(10)	6562(7)	32(2)
F(1E')	6560(12)	6553(11)	6773(8)	63(4)
F(2E')	5372(14)	7713(9)	6818(8)	46(3)
F(3E')	4765(14)	6261(10)	6883(7)	50(3)
O(1F)	7392(3)	7416(3)	9200(2)	50(1)
O(2F)	8876(3)	6454(3)	9536(2)	44(1)
C(1F)	8266(5)	6901(4)	9114(2)	36(1)
C(2F)	8685(5)	6791(4)	8396(3)	44(1)
F(1F)	7912(4)	7115(3)	7934(2)	81(1)
F(2F)	9658(4)	7283(4)	8306(2)	96(2)
F(3F)	8873(4)	5896(2)	8233(2)	66(1)
O(1M1)	11210(3)	5998(3)	9579(2)	48(1)
C(1M1)	11556(6)	5740(5)	8966(4)	71(2)
O(1M2)	8499(4)	6452(3)	5555(2)	50(1)
C(1M2)	8222(7)	6223(7)	6188(4)	89(2)

A.9 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **35**

	x	y	z	U(eq)
C(01)	2419(12)	-513(2)	2368(2)	13(1)
C(02)	3545(12)	-468(2)	2794(2)	16(1)
C(03)	3536(12)	-1096(2)	3001(2)	23(2)
C(04)	5013(12)	-1574(3)	2754(2)	20(2)
C(05)	3895(12)	-1614(2)	2328(2)	16(1)
C(06)	3899(12)	-990(2)	2123(2)	16(1)
N(07)	2192(11)	-14(2)	3034(1)	21(1)
C(08)	3532(14)	369(3)	3290(2)	21(2)
N(09)	1912(10)	705(2)	3534(1)	20(1)
C(10)	2916(13)	1072(2)	3866(2)	15(1)
C(11)	1518(12)	865(2)	4259(2)	13(1)
N(12)	1746(10)	206(2)	4302(1)	18(1)
C(13)	-334(13)	-174(3)	4258(2)	13(1)
N(14)	247(9)	-787(2)	4276(1)	15(1)
C(15)	-1755(12)	-1259(3)	4272(2)	15(1)
C(16)	-1915(11)	-1592(2)	4677(2)	11(1)
C(17)	-4069(12)	-2077(2)	4668(2)	16(1)
C(18)	-3711(13)	-2526(3)	4320(2)	21(2)
C(19)	-3500(12)	-2197(3)	3919(2)	22(2)
C(20)	-1349(12)	-1716(3)	3929(2)	20(2)
N(21)	-2311(10)	-1183(2)	5017(1)	16(1)
C(22)	-338(13)	-956(3)	5236(2)	16(1)
O(23)	1962(8)	-1048(2)	5153(1)	17(1)
O(29)	-1210(8)	-629(2)	5548(1)	16(1)
C(25)	629(12)	-319(3)	5826(2)	16(1)

C(26)	2193(12)	153(3)	5595(2)	22(2)
C(27)	-1208(13)	0(3)	6124(2)	23(2)
C(28)	2276(12)	-792(2)	6044(2)	19(2)
N(37)	2501(10)	93(2)	2177(1)	16(1)
C(31)	376(12)	459(3)	2191(2)	14(1)
C(33)	-871(12)	1543(3)	2160(2)	16(1)
C(34)	-2443(12)	1506(3)	2546(2)	21(2)
C(35)	846(12)	2116(2)	2164(2)	25(2)
C(36)	-2521(12)	1527(3)	1783(2)	21(2)
O(37)	1101(7)	1048(2)	2146(1)	14(1)
O(38)	-1851(8)	280(2)	2225(1)	17(1)
C(38)	2570(12)	1763(3)	3785(2)	13(1)
C(39)	514(13)	1984(3)	3557(2)	21(2)
C(40)	278(13)	2603(3)	3480(2)	24(2)
C(41)	2087(13)	3012(3)	3630(2)	25(2)
C(42)	4136(13)	2802(3)	3858(2)	22(2)
C(43)	4355(13)	2181(3)	3938(2)	18(1)
C(44)	2501(12)	1197(2)	4633(2)	11(1)
C(45)	1108(12)	1689(2)	4786(2)	14(1)
C(46)	1835(12)	1982(2)	5140(2)	15(1)
C(47)	4052(12)	1788(3)	5344(2)	17(1)
C(48)	5494(12)	1310(3)	5188(2)	17(1)
C(49)	4721(12)	1014(3)	4839(2)	15(1)
O(51)	-2561(9)	12(2)	4207(1)	19(1)
O(52)	5930(9)	401(2)	3302(1)	23(1)

A.10 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **36**

	x	y	z	U(eq)
N(1)	4875(1)	7238(1)	5751(1)	37(1)
C(2)	6077(2)	6852(1)	5824(2)	41(1)
C(3)	7016(2)	7050(1)	7020(2)	55(1)
C(4)	8235(2)	6657(2)	7050(3)	69(1)
C(5)	8684(2)	6953(2)	6018(2)	61(1)
C(6)	7739(2)	6774(1)	4820(2)	50(1)
C(7)	6499(2)	7140(1)	4761(1)	33(1)
N(8)	5576(2)	6950(1)	3635(1)	38(1)
O(9)	5799(1)	8174(1)	2754(1)	40(1)
C(9)	5382(2)	7471(1)	2665(2)	36(1)
N(10)	4660(2)	7158(1)	1624(1)	54(1)
C(11)	4452(2)	7589(1)	468(2)	43(1)
C(12)	4989(2)	7087(1)	-396(1)	38(1)
N(13)	4328(2)	6312(1)	-729(1)	40(1)
O(14)	3623(1)	6587(1)	-2752(1)	38(1)
C(14)	3608(2)	6156(1)	-1868(1)	31(1)
N(15)	2876(1)	5485(1)	-1984(1)	34(1)
C(16)	1969(2)	5273(1)	-3090(1)	30(1)
C(17)	811(2)	4951(1)	-2826(2)	42(1)
C(18)	-185(2)	4699(1)	-3980(2)	51(1)
C(19)	291(2)	4068(1)	-4693(2)	50(1)
C(20)	1429(2)	4395(1)	-4996(2)	42(1)
C(21)	2400(2)	4618(1)	-3830(2)	32(1)
N(22)	3522(2)	4919(1)	-4112(1)	40(1)
C(23)	3145(2)	7812(2)	-114(2)	55(1)

C(24)	2073(7)	7394(8)	-114(14)	76(2)
C(25)	943(8)	7601(9)	-766(15)	81(3)
C(26)	838(9)	8332(7)	-1487(10)	73(2)
C(27)	1841(7)	8748(7)	-1561(11)	62(2)
C(28)	3018(9)	8531(11)	-810(20)	64(2)
C(23')	3145(2)	7812(2)	-114(2)	55(1)
C(24')	2260(7)	7272(7)	71(12)	67(2)
C(25')	1065(8)	7360(9)	-473(15)	78(2)
C(26')	699(7)	8051(6)	-1246(11)	67(2)
C(27')	1509(7)	8579(7)	-1479(11)	62(2)
C(28')	2774(8)	8461(11)	-935(19)	58(2)
C(29)	6368(2)	6958(1)	142(2)	47(1)
C(30)	6877(6)	6239(4)	748(5)	67(2)
C(31)	8135(7)	6186(6)	1293(7)	97(3)
C(32)	8848(9)	6887(7)	1281(15)	87(4)
C(33)	8368(9)	7587(7)	605(15)	61(2)
C(34)	7110(8)	7638(5)	99(9)	41(2)
C(29')	6368(2)	6958(1)	142(2)	47(1)
C(30')	6866(6)	6155(4)	272(5)	65(2)
C(31')	8126(7)	6019(6)	707(7)	91(3)
C(32')	8885(8)	6714(7)	969(15)	84(4)
C(33')	8408(8)	7510(7)	878(15)	63(3)
C(34')	7162(8)	7633(5)	408(9)	46(2)
C(1A)	2874(3)	5250(2)	1348(2)	71(1)
O(1A)	3353(2)	5041(1)	548(1)	66(1)
O(2A)	3185(3)	5818(2)	2077(2)	153(2)
C(2A)	1800(2)	4741(1)	1428(2)	50(1)
F(1A)	972(2)	4598(2)	354(1)	86(1)
F(2A)	1102(2)	5088(1)	2088(2)	74(1)
F(3A)	2115(2)	4035(1)	1941(3)	89(1)
F(1A')	2107(9)	4520(8)	2557(8)	84(3)

F(2A')	1778(9)	4047(6)	773(9)	81(3)
F(3A')	1027(11)	5238(8)	1109(13)	110(4)
C(1B)	5219(2)	4508(1)	4148(2)	49(1)
O(1B)	4711(1)	3922(1)	4521(1)	47(1)
O(2B)	5199(2)	5248(1)	4376(2)	101(1)
C(2B)	5976(2)	4250(1)	3328(2)	53(1)
F(1B)	5284(2)	3755(1)	2441(1)	74(1)
F(2B)	6353(2)	4861(1)	2776(1)	73(1)
F(3B)	6902(2)	3767(1)	3852(2)	89(1)

A.11 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **37**

	x	y	z	U(eq)
N(1)	17097(3)	33(1)	12070(1)	34(1)
C(2)	16763(3)	599(1)	11844(1)	32(1)
C(3)	16719(4)	1046(2)	12275(1)	37(1)
C(4)	16314(5)	1634(2)	12055(2)	53(1)
C(5)	14948(5)	1595(2)	11774(2)	61(1)
C(6)	14984(4)	1152(2)	11334(2)	47(1)
C(7)	15421(3)	562(1)	11536(1)	32(1)
N(8)	15524(3)	151(1)	11110(1)	31(1)
O(9)	13861(3)	-437(1)	11418(1)	42(1)
C(9)	14724(3)	-316(1)	11073(1)	28(1)
N(10)	14906(3)	-637(1)	10637(1)	30(1)
C(11)	14217(4)	-1187(2)	10562(3)	26(1)
C(12)	15249(5)	-1618(2)	10357(3)	36(1)
C(13)	14585(6)	-2188(2)	10221(4)	55(2)
C(14)	13406(5)	-2115(3)	9846(3)	61(2)
C(15)	12350(4)	-1689(2)	10064(3)	55(2)
C(16)	13006(4)	-1120(2)	10191(3)	34(1)
C(11')	14175(19)	-1128(8)	10423(10)	24(9)
C(12')	15140(20)	-1559(8)	10181(9)	19(7)
C(13')	14340(30)	-2104(9)	10016(9)	28(7)
C(14')	13280(20)	-1941(9)	9614(8)	28(6)
C(15')	12280(20)	-1482(11)	9822(13)	60(10)
C(16')	13010(17)	-970(9)	10054(7)	19(7)
N(17)	11993(3)	-722(1)	10409(1)	36(1)
O(18)	12381(3)	45(2)	9870(1)	59(1)

C(18)	11830(3)	-169(2)	10271(1)	37(1)
N(19)	10986(3)	141(1)	10580(1)	35(1)
C(20)	10661(3)	734(2)	10496(1)	33(1)
C(21)	9174(4)	804(2)	10288(1)	39(1)
N(22)	8983(4)	465(2)	9816(1)	55(1)
O(23)	7230(3)	-61(1)	10120(1)	49(1)
C(23)	8018(3)	50(2)	9762(1)	34(1)
N(24)	7995(3)	-214(2)	9284(1)	49(1)
C(25)	7131(4)	-696(2)	9157(1)	40(1)
C(26)	7917(6)	-1262(2)	9151(2)	65(1)
C(27)	7059(7)	-1782(2)	8996(2)	71(2)
C(28)	6321(7)	-1682(2)	8476(2)	73(2)
C(29)	5517(6)	-1124(2)	8500(2)	54(1)
C(30)	6439(4)	-608(1)	8617(1)	37(1)
N(31)	5666(3)	-78(1)	8616(1)	32(1)
O(32)	5626(2)	4(1)	7720(1)	32(1)
C(32)	5268(3)	181(1)	8166(1)	26(1)
N(33)	4440(3)	637(1)	8224(1)	29(1)
C(34)	4202(3)	1058(1)	7813(1)	27(1)
C(35)	4157(4)	1659(1)	8059(2)	38(1)
C(36)	3855(4)	2123(1)	7652(2)	42(1)
C(37)	2504(4)	1998(1)	7375(2)	38(1)
C(38)	2556(4)	1416(1)	7110(2)	37(1)
C(39)	2900(3)	946(1)	7503(1)	30(1)
N(40)	3048(3)	397(1)	7198(1)	37(1)
C(41)	10873(3)	1082(1)	10998(1)	31(1)
C(42)	10526(4)	863(2)	11488(1)	35(1)
C(43)	10671(4)	1185(2)	11946(2)	49(1)
C(44)	11152(5)	1736(2)	11915(2)	59(1)
C(45)	11487(4)	1970(2)	11428(3)	65(2)
C(46)	11355(4)	1648(2)	10972(2)	44(1)

C(47)	8792(7)	1447(3)	10244(3)	43(2)
C(48)	8084(5)	1723(2)	10643(2)	42(1)
C(49)	7762(6)	2296(2)	10601(3)	60(2)
C(50)	8126(7)	2596(3)	10166(4)	86(3)
C(51)	8841(11)	2341(5)	9769(5)	96(4)
C(52)	9199(5)	1762(3)	9801(3)	69(2)
C(47')	9010(40)	1358(11)	10027(11)	38(9)
C(48')	8450(30)	1733(11)	10389(11)	40(7)
C(49')	8330(40)	2309(11)	10265(12)	60(8)
C(50')	8900(70)	2491(13)	9802(17)	70(14)
C(51')	9520(40)	2129(10)	9453(11)	69(9)
C(52')	9580(30)	1542(9)	9544(9)	42(6)
C(1A1)	8900(4)	-963(1)	11305(1)	34(1)
O(1A1)	7720(3)	-852(2)	11414(2)	76(1)
O(2A1)	9954(3)	-674(1)	11367(1)	43(1)
C(2A1)	9071(4)	-1545(2)	11036(2)	43(1)
F(1A1)	8944(3)	-1495(1)	10516(1)	66(1)
F(2A1)	10279(3)	-1784(1)	11128(1)	70(1)
F(3A1)	8145(3)	-1925(1)	11180(2)	86(1)
C(1A2)	9582(5)	626(2)	8231(2)	60(1)
O(1A2)	10068(6)	634(2)	8678(1)	99(2)
O(2A2)	9702(4)	253(2)	7883(1)	69(1)
C(2A2)	8782(6)	1168(2)	8064(2)	76(2)
F(1A2)	9415(6)	1634(2)	8178(3)	132(3)
F(2A2)	7624(5)	1173(3)	8312(4)	164(4)
F(3A2)	8478(14)	1174(3)	7557(3)	183(5)
F(4A2)	7713(15)	1028(7)	7815(7)	72(5)
F(5A2)	9414(15)	1457(7)	7674(6)	72(5)
F(6A2)	8450(30)	1556(10)	8418(8)	135(10)
O(1E1)	11586(13)	-1420(3)	8326(3)	188(4)
C(1E1)	11309(15)	-1928(4)	8449(5)	168(5)

C(2E1)	11202(16)	-2420(4)	8066(5)	207(7)
O(1E2)	4348(6)	634(2)	9421(1)	111(2)
C(1E2)	5022(7)	1030(2)	9771(2)	72(2)
C(2E2)	5729(5)	1455(2)	9460(2)	63(1)
O(1W)	11906(5)	-494(2)	7699(2)	62(1)
O(1W')	12720(11)	-562(4)	7975(5)	62(1)
O(3W)	11341(9)	-446(3)	8939(2)	163(3)
O(2W)	2044(11)	1248(5)	9107(3)	117(4)

A.12 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **41**

	x	y	z	U(eq)
N(1A)	8397(3)	5267(3)	3869(3)	30(1)
C(2A)	8575(4)	6337(3)	3512(3)	27(1)
C(3A)	8430(3)	7117(3)	4371(3)	26(1)
N(4A)	7194(3)	7455(3)	5060(2)	26(1)
C(5A)	6971(3)	7060(3)	5960(3)	22(1)
N(6A)	5776(3)	7527(3)	6533(2)	22(1)
C(7A)	5328(3)	7017(3)	7416(3)	22(1)
C(8A)	4099(3)	6917(3)	7389(3)	24(1)
N(9A)	4357(3)	6208(3)	6487(2)	24(1)
C(10A)	3647(4)	6499(3)	5878(3)	25(1)
N(11A)	4180(3)	5866(3)	4989(2)	28(1)
C(12A)	3612(4)	6057(3)	4184(3)	28(1)
C(13A)	4037(4)	6868(4)	3508(3)	33(1)
N(14A)	3614(3)	8008(3)	4032(3)	32(1)
C(15A)	9838(4)	6015(3)	2740(3)	33(1)
C(16A)	10092(4)	7067(4)	2399(3)	38(1)
C(17A)	9980(4)	7832(4)	3265(3)	41(1)
C(18A)	8693(4)	8187(4)	4016(3)	36(1)
O(19A)	7788(2)	6343(2)	6223(2)	25(1)
C(20A)	5168(3)	7668(4)	8350(3)	28(1)
C(21A)	4627(4)	8860(4)	8482(3)	36(1)
C(22A)	4510(4)	9431(5)	9347(4)	50(1)
C(23A)	4923(4)	8860(5)	10068(4)	53(2)
C(24A)	5441(4)	7689(5)	9959(3)	45(1)
C(25A)	5581(4)	7092(4)	9101(3)	33(1)

C(26A)	3521(3)	6443(3)	8298(3)	23(1)
C(27A)	4133(4)	5359(4)	8526(3)	31(1)
C(28A)	3592(4)	4949(4)	9368(3)	34(1)
C(29A)	2428(4)	5591(4)	9970(3)	35(1)
C(30A)	1817(4)	6655(4)	9741(3)	35(1)
C(31A)	2365(4)	7090(3)	8916(3)	26(1)
O(32A)	2599(2)	7264(2)	6098(2)	26(1)
C(33A)	3953(5)	4904(4)	3630(4)	43(1)
C(34A)	3491(5)	5046(5)	2716(4)	58(2)
C(35A)	3971(5)	5824(5)	2053(4)	60(2)
C(36A)	3601(4)	6975(4)	2599(3)	43(1)
N(1B)	-1137(3)	14200(3)	6742(2)	27(1)
C(2B)	-59(3)	14141(3)	7080(3)	25(1)
C(3B)	1018(4)	14159(3)	6215(3)	26(1)
N(4B)	1428(3)	13180(3)	5494(2)	28(1)
C(5B)	1111(3)	13265(3)	4649(3)	25(1)
N(6B)	1629(3)	12264(3)	4041(2)	27(1)
C(7B)	1111(4)	12103(3)	3269(3)	28(1)
C(8B)	1056(4)	10894(3)	3324(3)	26(1)
N(9B)	150(3)	10921(3)	4263(2)	27(1)
C(10B)	285(3)	10031(3)	4808(3)	23(1)
N(11B)	-599(3)	10273(3)	5706(2)	28(1)
C(12B)	-673(4)	9416(3)	6394(3)	25(1)
C(13B)	-192(3)	9585(3)	7224(3)	24(1)
N(14B)	1132(3)	9488(3)	6833(2)	25(1)
C(15B)	-471(4)	15137(4)	7867(3)	32(1)
C(16B)	582(4)	15119(4)	8229(3)	38(1)
C(17B)	1669(4)	15137(4)	7384(3)	34(1)
C(18B)	2086(4)	14141(4)	6588(3)	32(1)
O(19B)	412(2)	14172(2)	4458(2)	28(1)
C(20B)	1766(4)	12313(3)	2265(3)	31(1)

C(21B)	3040(4)	11928(4)	1930(3)	38(1)
C(22B)	3628(5)	12073(4)	963(4)	51(1)
C(23B)	2930(7)	12602(4)	364(4)	59(2)
C(24B)	1664(6)	13017(4)	703(4)	55(2)
C(25B)	1090(5)	12870(4)	1652(3)	40(1)
C(26B)	776(4)	10492(3)	2457(3)	28(1)
C(27B)	1723(4)	9787(3)	1679(3)	34(1)
C(28B)	1501(5)	9415(5)	879(4)	49(1)
C(29B)	324(6)	9770(5)	819(4)	52(1)
C(30B)	-650(5)	10494(5)	1580(4)	50(1)
C(31B)	-409(4)	10839(4)	2403(3)	37(1)
O(32B)	1114(2)	9077(2)	4550(2)	28(1)
C(33B)	-2005(4)	9490(4)	6824(3)	34(1)
C(34B)	-2100(4)	8625(4)	7550(3)	37(1)
C(35B)	-1597(4)	8773(4)	8374(3)	39(1)
C(36B)	-278(4)	8736(3)	7978(3)	30(1)
O(1A1)	7152(3)	13843(3)	8325(3)	48(1)
O(2A1)	8833(3)	12359(3)	8268(3)	51(1)
C(1A1)	7752(4)	12947(4)	8604(3)	34(1)
C(2A1)	6980(5)	12497(5)	9463(4)	50(1)
F(1A1)	6173(3)	13323(3)	10154(2)	69(1)
F(2A1)	7663(3)	11707(3)	9886(3)	87(1)
F(3A1)	6313(3)	12017(3)	9128(3)	77(1)
O(1A2)	2564(3)	10653(3)	5522(2)	37(1)
O(2A2)	4061(3)	9015(2)	5620(2)	44(1)
C(1A2)	3630(4)	10058(4)	5540(3)	35(1)
C(2A2)	4499(5)	10698(4)	5475(5)	55(2)
F(1A2)	5665(3)	10062(2)	5019(3)	88(1)
F(2A2)	4223(3)	11640(3)	5059(4)	92(1)
F(3A2)	4468(4)	11007(4)	6369(4)	115(2)
O(1A3)	4442(4)	9686(4)	3069(4)	86(2)

O(2A3)	6143(4)	8071(5)	2724(4)	107(2)
C(1A3)	5543(6)	9096(8)	2687(6)	97(3)
C(2A3)	6337(6)	9804(7)	2148(6)	118(4)
F(1A3)	5917(5)	10476(6)	1608(5)	92(2)
F(2A3)	7471(6)	8992(6)	1467(7)	145(3)
F(3A3)	6677(9)	10288(8)	2823(5)	123(3)
F(4A3)	7267(13)	9488(17)	2387(14)	92(2)
F(5A3)	5709(16)	11001(13)	2555(17)	145(3)
F(6A3)	6470(20)	9710(20)	1171(11)	123(3)
O(1A4)	6687(2)	14563(2)	5316(2)	37(1)
O(2A4)	8258(3)	12968(2)	5371(2)	40(1)
C(1A4)	7188(4)	13515(4)	5376(3)	31(1)
C(2A4)	6349(4)	12848(4)	5503(3)	55(2)
F(1A4)	6729(5)	11806(4)	5632(8)	93(3)
F(2A4)	5274(5)	13380(6)	6085(7)	101(3)
F(3A4)	6091(9)	12835(7)	4586(6)	127(3)
F(4A4)	5216(9)	13327(9)	5629(14)	93(3)
F(5A4)	6808(10)	11953(11)	4906(11)	101(3)
F(6A4)	6408(15)	12382(14)	6416(10)	127(3)
O(1S1)	7613(5)	4536(4)	2428(3)	89(2)
C(1S1)	7519(7)	3614(7)	1953(8)	129(4)
O(1S2)	10926(3)	10744(3)	8484(3)	51(1)
C(1S2)	11491(6)	11351(6)	8864(5)	82(2)
O(1S3)	7331(5)	6321(6)	1443(3)	107(2)
C(1S3)	8318(8)	6377(10)	596(5)	132(4)

A.13 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **53**

	x	y	z	U(eq)
N(1)	6522(6)	6820(1)	745(1)	29(1)
O(2)	3 698(5)	5936(1)	458(1)	28(1)
C(2)	5379(7)	6182(2)	781(2)	26(1)
N(2)	6490(5)	5837(1)	1274(1)	22(1)
C(3)	9417(7)	6271(2)	2124(1)	30(1)
C(4)	11683(7)	6787(2)	2191(1)	33(1)
C(5)	11270(7)	7504(2)	1889(2)	38(1)
C(6)	10251(7)	7452(2)	1263(2)	34(1)
C(7)	8728(7)	6254(2)	1477(1)	26(1)
C(8)	7937(7)	6979(2)	1280(2)	29(1)
O(9)	8791(5)	4836(1)	1455(1)	26(1)
C(9)	6702(8)	5099(2)	1313(1)	22(1)
N(10)	4533(6)	4742(1)	1199(1)	22(1)
C(11)	2689(6)	3702(2)	738(1)	26(1)
C(12)	2519(7)	2901(1)	745(1)	28(1)
C(13)	1698(7)	2642(2)	1349(1)	28(1)
C(14)	3574(7)	2910(1)	1816(1)	26(1)
C(15)	4485(7)	3980(1)	1218(1)	22(1)
C(16)	3643(7)	3710(1)	1821(1)	22(1)
N(17)	5324(5)	3982(1)	2278(1)	24(1)
O(18)	2029(5)	4283(1)	2904(1)	28(1)
C(18)	4360(8)	4285(2)	2779(1)	22(1)
N(19)	6232(5)	4578(1)	3123(1)	25(1)
C(20)	4844(7)	5700(2)	3556(1)	28(1)
C(21)	4297(6)	6088(2)	4132(1)	29(1)

C(22)	6599(7)	6036(2)	4546(1)	25(1)
C(23)	7273(7)	5268(2)	4660(1)	28(1)
C(24)	5585(7)	4937(2)	3667(1)	24(1)
C(25)	7883(7)	4896(2)	4088(1)	23(1)
N(26)	8509(6)	4158(1)	4209(1)	33(1)
O(1W)	5643(5)	8246(1)	413(1)	38(1)

A.14 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **59**

	x	y	z	U(eq)
N(1A)	2255(7)	3826(3)	-829(2)	26(1)
C(2A)	2403(9)	2530(4)	-902(2)	23(1)
C(3A)	1151(9)	1881(4)	-385(2)	28(1)
N(4A)	2241(7)	2289(3)	144(2)	27(1)
C(5A)	889(8)	2434(5)	647(2)	28(1)
S(5A)	-2209(2)	1999(1)	724(1)	39(1)
N(6A)	2183(7)	2915(4)	1073(2)	29(1)
C(7A)	1208(9)	3087(4)	1662(2)	27(1)
C(8A)	2961(9)	2447(4)	2088(2)	23(1)
N(9A)	2970(7)	1165(3)	1991(2)	28(1)
O(10A)	7252(6)	864(3)	2136(1)	28(1)
C(10A)	5118(9)	490(4)	2036(2)	24(1)
O(11A)	4563(5)	-678(3)	1947(1)	28(1)
C(12A)	6616(9)	-1575(4)	1878(2)	32(1)
C(13A)	8247(9)	-1685(5)	2406(2)	34(1)
C(14A)	5160(10)	-2737(5)	1806(3)	45(2)
C(15A)	8225(10)	-1272(5)	1325(2)	37(1)
O(16A)	6474(6)	4100(3)	-683(2)	32(1)
C(16A)	4271(10)	4451(5)	-655(2)	28(1)
O(17A)	3484(6)	5545(3)	-468(2)	33(1)
C(18A)	5383(10)	6382(5)	-251(3)	38(1)
C(19A)	6705(10)	5816(5)	266(2)	42(2)
C(20A)	3622(11)	7424(5)	-44(3)	61(2)
C(21A)	7148(11)	6803(5)	-725(3)	52(2)
C(22A)	1170(10)	2148(4)	-1453(2)	32(1)

C(23A)	1331(11)	788(4)	-1519(2)	38(1)
C(24A)	141(10)	124(5)	-1003(2)	37(1)
C(25A)	1358(10)	516(4)	-447(2)	34(1)
C(26A)	982(9)	4432(4)	1780(2)	30(1)
C(27A)	108(10)	4654(4)	2402(2)	36(1)
C(28A)	1921(9)	4054(4)	2818(2)	29(1)
C(29A)	2080(9)	2706(4)	2712(2)	26(1)
N(1B)	1088(8)	8980(4)	7081(2)	34(1)
C(2B)	1078(9)	7705(4)	7227(2)	30(1)
C(3B)	2728(9)	7001(5)	6 793(2)	31(1)
N(4B)	1759(8)	7207(4)	6218(2)	38(1)
C(5B)	3129(17)	7146(10)	5726(4)	31(2)
S(5B)	6221(5)	6666(3)	5729(1)	42(1)
N(6B)	1871(8)	7639(4)	5258(2)	44(1)
N(4B')	1759(8)	7207(4)	6218(2)	38(1)
C(5B')	3152(18)	7734(10)	5766(4)	31(2)
S(5B')	6219(5)	8232(3)	5756(1)	38(1)
N(6B')	1871(8)	7639(4)	5258(2)	44(1)
C(7B)	3012(10)	7974(5)	4698(2)	36(1)
C(8B)	1493(9)	7400(4)	4228(2)	26(1)
N(9B)	1458(7)	6107(3)	4287(2)	30(1)
O(10B)	-2793(6)	5848(3)	4258(2)	42(1)
C(10B)	-654(10)	5446(4)	4318(2)	25(1)
O(11B)	-83(5)	4269(3)	4402(2)	28(1)
C(12B)	-2161(10)	3376(4)	4486(2)	33(1)
C(13B)	-3686(9)	3308(5)	3945(2)	39(1)
C(14B)	-655(10)	2218(5)	4576(3)	49(2)
C(15B)	-3766(9)	3681(5)	5022(2)	40(2)
O(16B)	-3158(6)	9294(3)	7118(2)	46(1)
C(16B)	-1005(10)	9647(4)	7031(2)	27(1)
O(17B)	-333(6)	10793(3)	6891(2)	32(1)

C(18B)	-2352(10)	11702(5)	6762(2)	36(1)
C(19B)	-3796(10)	11334(5)	6247(2)	40(1)
C(20B)	-772(10)	12822(5)	6611(3)	49(2)
C(21B)	-4052(10)	11905(5)	7296(3)	44(2)
C(22B)	1918(10)	7458(5)	7839(2)	36(1)
C(23B)	2001(12)	6127(5)	7989(3)	48(2)
C(24B)	3691(12)	5456(5)	7565(3)	53(2)
C(25B)	2748(12)	5656(5)	6944(3)	50(2)
C(26B)	3093(11)	9342(5)	4621(3)	51(2)
C(27B)	4162(12)	9677(5)	4009(3)	59(2)
C(28B)	2640(11)	9131(5)	3552(3)	52(2)
C(29B)	2582(11)	7778(5)	3630(2)	38(1)

A.15 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **61**

	x	y	z	U(eq)
C(1)	10381(1)	4430(2)	411(1)	35(1)
C(2)	10966(2)	5320(2)	97(2)	39(1)
C(3)	11513(2)	5472(2)	-652(2)	48(1)
C(4)	11480(2)	4733(2)	-1103(2)	52(1)
C(5)	10910(2)	3845(2)	-795(2)	52(1)
C(6)	10367(2)	3694(2)	-39(2)	42(1)
C(7)	9744(1)	4239(1)	1209(1)	33(1)
N(8)	9205(1)	4697(1)	1106(1)	37(1)
O(9)	7809(1)	3387(1)	1066(1)	40(1)
C(9)	8273(2)	4235(2)	1075(1)	34(1)
N(10)	7882(1)	4774(1)	1030(1)	42(1)
C(11)	6889(2)	4373(2)	1106(2)	41(1)
C(12)	6432(2)	4252(2)	188(2)	53(1)
C(13)	5392(2)	3847(2)	275(2)	58(1)
C(14)	5173(2)	4419(2)	912(2)	57(1)
C(15)	5633(2)	4540(2)	1828(2)	50(1)
C(16)	6674(2)	4982(2)	1708(1)	42(1)
N(17)	7137(1)	5157(2)	2579(1)	41(1)
O(18)	8379(1)	6522(1)	2174(1)	54(1)
C(18)	7921(2)	5952(2)	2776(2)	42(1)
N(19)	8174(1)	6073(1)	3649(1)	46(1)
C(20)	8949(2)	6894(2)	4031(3)	55(1)
C(21)	8673(3)	7143(3)	4908(3)	70(1)
C(22)	9488(3)	7990(4)	5346(4)	84(1)

C(23)	10293(3)	7832(5)	5457(4)	87(1)
C(24)	10590(3)	7608(4)	4550(5)	85(1)
C(25)	9779(3)	6765(3)	4140(4)	65(1)
C(20')	9024(3)	6890(3)	3922(5)	56(2)
C(21')	8834(5)	7644(4)	4201(7)	67(2)
C(22')	9707(7)	8503(4)	4537(8)	84(2)
C(23')	10166(7)	8252(7)	5271(7)	86(2)
C(24')	10386(6)	7503(6)	4963(9)	77(2)
C(25')	9506(6)	6661(5)	4660(8)	68(2)
O(1W)	10000	6648(2)	1667	62(1)

Bibliography

(1) Boman, H. G. *Ann. Rev. Immunol.* **1995**, *13*, 61.
(2) Hancock, R. E. W.; Farmer, S. W. *Antimicrob. Agents Chemother.* **1993**, *37*, 453.
(3) Hancock, R. E. W. *Lancet* **1997**, *349*, 418.
(4) Matsuzaki, K.; Sugishita, K.; Harada, M.; Fujii, N.; Miyajima, K. *Biochim. Biophys. Acta* **1997**, *1327*, 119.
(5) Hill, D.; Mio, M.; Prince, R.; Hughes, T.; Moore, J. *Chem. Rev*. **2001**, *101*, 3893.
(6) Rizo, J.; Gierasch, L. M. *Ann. Rev. Biochem.* **1992**, *61*, 387.
(7) Schneider, J. P.; Kelly, J. W. *Chem. Rev.* **1995**, *95*, 2169.
(8) Nowick, J. S.; Smith, E. M.; Pairish, M. *Chem. Soc. Rev.* **1996**, *25*, 401.
(6) Applequist, J.; Bode, K.; Appella, D.; Christianson, L.; Gellman, S. *J. Am. Chem. Soc*. **1998**, *120*, 4891.
(7) Porter, E. A.; Wang, X.; Lee, H. S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 298.
(8) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc*. **2002**, *124*, 7324.
(9) Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9367.
(10) Mohle, K.; Hofmann, H.-J. *Biopolymers* **1996**, *38*, 781.
(11) Kirshenbaum, K.; Barron, A. E.; Goldsmith, R. A.; Armand, P.; Bradley, E. K.; Truong, K. T. V.; Dill, K. A.; Cohen, F. E.; Zuckermann, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4303.
(12) Armand, P.; Kirshenbaum, K.; Falicov, A.; Dunbrack, R. L.; Dill, K. A.; Zuckermann, R. N.; Cohen, F. E. *Folding Des.* **1997**, *2*, 369.
(13) Smith, A. B., III; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672.
(14) Smith, A. B., III; Guzman, M. C.; Sprengeler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947.
(15) Lucarini, S.; Tomasini, C. *J. Org. Chem.* **2001**, *66*, 727.
(16) Graf, R.; Lohaus, G.; Borner, K.; Schmidt, E.; Bestian, H. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 481.
(17) Kovacs, J.; Ballina, R.; Rodin, R. L.; Balasubramanian, D.; Applequist, J. *J. Am. Chem. Soc.* **1965**, *87*, 119.
(18) Bestian, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 278.
(19) Schmidt, V. E. *Angew. Makromol. Chem.* **1970**, *14*, 185.
(20) Matthews, J. L.; Overhand, M.; Kuhnle, F. N. M.; Ciceri, P. E.; Seebach, D. *Liebigs Ann.* **1997**, 1371.
(21) Seebach, D.; Matthews, J. L.; Meden, A.; Wessels, T.; Baerlocher, C.; McCusker, L. B. *Helv. Chim. Acta* **1997**, *80*, 173.
(22) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913.
(23) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015.
(24) Seebach, D.; Albert, M.; Arvidsson, P. I.; Rueping, M.; Schreiber, J. V. *Chimia* **2001**, *55*, 345.
(25) Yang, D.; Ng, F.-F.; Li, Z.-J. *J. Am. Chem. Soc.* **1996**, *118*, 9794.

(26) Gennari, C.; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2067.
(27) Moree, W. J.; van der Marel, G. A.; Liskamp, R. J. *J. Org. Chem.* **1995**, *60*, 5157.
(28) Gude, M.; Piarilli, U.; Potenza, D.; Salom, B.; Gennari, C. *Tetrahedron Lett.* **1996**, *37*, 8589.
(29) Monnee, M. C. F.; Marijine, M. F.; Brouwer, A. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **2000**, *41*, 7991.
(30) Gunther, R.; Hofmann, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 247.
(31) Kajtar, M.; Bruckner, V. *Tetrahedron Lett.* **1966**, *7*, 4813.
(32) Kajtar, M.; Hollosi, M. *Acta Chim. Acad. Sci. Hung.* **1970**, *65*, 403.
(33) Rydon, H. N. *J. Chem. Soc.* **1964**, 1328.
(34) Watanabe, T.; Ina, T.; Ogawa, K.; Matsumoto, T.; Sawa, S.; Ono, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3939.
(35) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568.
(36) Moran, E. J.; Wilson, T. E.; Cho, C. Y.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P. A.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Biopolymers* **1995**, *37*, 213.
(37) Cho, C. Y.; Moran, E. J.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P. A.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science* **1993**, *261*, 1303.
(38) Cho, C. Y.; Youngquist, R. S.; Paikoff, S. J.; Beresini, M. H.; Herbert, A. R.; Berleau, L. T.; Liu, C. W.; Wemmer, D. E.; Keough, T.; Schultz, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7706.
(39) Lin, P.; Ganesan, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 511.
(40) von Roedern, E. G.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 687.
(41) von Roedern, E.G.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156.
(42) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S.; Sharma, J. A. R. P.; Ravikanth, V.; Diwan, P. V.; Nagaraj, R.; Kunwar, A. C. *J. Org. Chem.* **2000**, *65*, 6441.
(43) Szabo, L.; Smith, B. L.; McReynolds, K. D.; Parrill, A. L.; Morris, E. R.; Gervay, J. *J. Org. Chem.* **1998**, *63*, 1074.
(44) Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *Chem. Commun.* **1998**, 2041.
(45) Seebach, D.; Beck, A.; Rueping, M.; Schreiber, J. V.; Sellner, H. *Chimia* **2001,** 55, 98.
(46) Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1223.
(47) Werder, M.; Hauser, H.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1774.
(48) Porter, E. A.; Wang, X.; Lee, H.-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.
(49) Muller, H.-M.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 477.
(50) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071.
(51) Krauthauser, S.; Christianson, L. A.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1997**, *119*, 11719.
(52) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1595.
(53) Chung, Y. J.; Christianson, L. A.; Stanger, H. E.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 10555.

(54) Chung, Y. J.; Huck, B. R.; Christianson, L. A.; Stanger, H. E.; Krauthauser, S.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 3995.
(55) Huck, B. R.; Fisk, J. D.; Gellman, S. H. *Org. Lett.* **2000**, *2*, 2607.
(56) Hanessian, S.; Yang, H. *Tetrahedron Lett.* **1997**, *38*, 3155.
(57) Motorina, I. A.; Huel, C.; Quiniou, E.; Mispelter, J.; Adjadj, E.; Grierson, D. S. *J. Am. Chem. Soc.* **2001**, *123*, 8.
(58) Porter, E. A.; Wang, X.; Lee, H-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, 565.
(59) Matsuzaki, K.; Sugishita, K.-I.; Fujii, N. *Biochemistry* **1995,** *34*, 3423.
(60) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 7324.
(61) Raguse, T. L.; Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 12774.
(62) Gellman, S. H. *Acc. Chem. Res*. **1998**, *31*, 173.
(63) Sanford, A. R.; Yamato, K.; Yang, X.; Yuan, L.; Han, Y.; Gong, B. *Eur. J. Biochem.* **2004,** *271*, 1416.
(64) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, NY, 1953.
(65) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinhem, Germany, 1995.
(66) Dougherty, J. P.; Rizzo, C. J.; Breslow, R. *J. Am. Chem. Soc.* **1992**, *114*, 6254.
(67) Hashimoto, H.; Switzer, C. *J. Am. Chem. Soc.* **1992**, *114*, 6255.
(68) Kierzek, R.; He, L.; Turner, D. H. *Nucleic Acids Res.* **1992**, *20*, 1685.
(69) Bassani, D. M.; Lehn, J.-M. *Bull. Chem. Soc. Fr.* **1997**, *134*, 897.
(70) Bassani, D. M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1845.
(71) Ohkita, M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem. Eur. J.* **1999**, *5*, 3471.
(72) Ohkita, M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Heterocycles* **2000**, *52*, 103.
(73) Kagechika, H.; Azumaya, I.; Tanatani, A.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1999**, *40*, 3423.
(74) Lokey, R. S.; Iverson, B. L. *Nature* **1995**, *375*, 303.
(75) Archer, E. A.; Gong, H.; Krische, M. J. *Tetrahedron* **2001**, *57*, 1139.
(76) Nowick, J. S.; Chung, D. M.; Maitra, K.; Maitra, S.; Stigers, K. D.; Sun, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7654.
(77) Nowick, J. S.; Tsai, J. H.; Bui, Q.-C. D.; Maitra, S. *J. Am. Chem. Soc.* **1999**, *121*, 8409.
(78) Deetz, M. J.; Fahey, J. E.; Smith, B. D. *J. Phys. Org. Chem.* **2001,** *14*, 463.
(79) Creamer, T. P.; Rose, G. D. *Proc. Natl. Acad. Sci.* **1992,** *89*, 5937.
(80) Finer Moore, J. S.; Fauman, E. B.; Stroud, R. M. *Protein Eng.* **1996,** *9*, 69.
(81) Gallivan, J. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **2000,** *122*, 870.
(82) Jenkins, C. L.; Lin, G.; Duo, J.; Rapolu, D.; Guzei, I. A.; Raines, R. T.; Krow, G. R. *J. Org. Chem.* **2004,** *69*, 8565.
(83) Kelly, M. A.; Chellgren, B. W.; Rucker, A. L.; Troutman, J. M.; Fried, M. G.; Miller, A.-F.; Creamer, T. P. *Biochemistry* **2001,** *40*, 14376.
(84) Chellgren, B. W.; Creamer, T. P. *J. Am. Chem. Soc.* **2004,** *126*, 14734.
(85) Haushalter, K. A.; Lau, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1996,** *118*, 8891.
(86) Rabinovitz, M.; Pines, A. *J. Am. Chem. Soc.* **1969**, *91*, 1585.
(87) Vysotsky, M. O.; Pop, A.; Broda, F.; Thondorf, I.; Böhmer, V. *Chem. Eur. J.* **2001,** *7*, 4403.
(88) Motoshima, H.; Mine, S.; Masumoto, K.; Abe, Y.; Iwashita, H.; Hasimoto, Y.; Chijiiwa, Y.; Ueda, T.; Imoto, T. *J. Biochem.* **1997,** *121*, 1076.

(89) Joshi, H. V.; Meier, M. S. *J. Am. Chem. Soc.* **1996,** *118*, 12038.
(90) Munoz, V.; Serrano, L. *J. Mol. Biol.* **1995,** *245*, 275.
(91) Niwa, M.; Murata, T.; Kitamastu, M.; Matsumoto, T.; Higashi, N. *J. Mater. Chem.* **1999,** *9*, 343.
(92) Higashi, N.; Nishikawa, R.; Koga, T.; Niwa, M. *J. Colloid and Interface Sci.* **1999,** *220*, 362.
(93) Hart, S. A.; Bahadoor, A. B. F.; Matthews, E. E.; Qiu, X. Y. J.; Schepartz, A. *J. Am. Chem. Soc.* **2003,** *125*, 4022.
(94) Nowick, J. S.; Powell, N. A.; Martinez, E. J.; Smith, E. Em.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 3763.
(95) Nowick, J. S.; Abdi, M.; Bellamo, K. A.; Love, J. A.; Martinez, E. J.; Noronha, G.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 89.
(96) Nowick, J. S.; Mahrus, S.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 1066.
(97) Burgess, K.; Linthicum, D. S.; Shin, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 907.
(98) Wilson, M. E.; Nowick, J. S. *Tetrahedron Lett.* **1998**, *39*, 6613.
(99) Kim. J.; Bi, Y.; Paikoff, S. J.; Schultz, P. G. *Tetrahedron Lett.* **1996**, *37*, 5305.
(100) Semetey, V.; Rognan, D.; Hemmerlin, C.; Graff, R.; Briand, J-P.; Marraud, M.; Guichard, G. *Angew. Chem., Int. Ed*. *Engl.* **2002**, *41*, 1893.
(101) Hemmerlin, C.; Marraud, M.; Rognan, D.; Semetey, V.; Briand, J-P.; Guichard, G. *Helv. Chim. Acta* **2002**, *85*, 3692.
(102) Violette, A.; Averland-Petit, M. C.; Semetey, V.; Hemmerlin, C.; Casimir, R.; Graff, R.; Marraud, M.; Briand, J-P.; Rognan, D.; Guichard, G. *J. Am. Chem. Soc.* **2005**, *127*, 2156.
(103) Lam, P. Y. S.; Jadhaw, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C. H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson, -Viitanen, S. *Science* **1994**, *263*, 380.
(104) Chorev, M.; Goodman, M. *Acc. Chem. Res*. **1996**, *26*, 266.
(105) Tamilarasu, N.; Huq, I.; Rana, T. M. *J. Am. Chem. Soc.* **1999**, *121*, 1597.
(106) Bobde, V.; Sasidhar, Y. U.; Durani, S. *Int. J. Peptide Protein Res*. **1994**, *43*, 209.
(107) Aravinda, S.; Shamala, N.; Desiraju, S.; Balaram, P. *Chem. Commun.* **2004**, 2454.
(108) Leach, A. R. Molecular Modeling: Principles and Applications; 2nd Edition, 2001.
(109) Lewars, E. *Computational Chemistry: Introduction to the Theory and Applications of Molecular and Quantum Mechanics;* Kluwer Academic Publishers, 2003.
(110) http://cmm.cit.nih.gov/modeling/guide_documents/molecular_mechanics_document.html.
(111) MacroModel 8.1 User Manual.
(112) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S. Jr.; Weiner, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 765.
(113) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M. Jr.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179.
(114) Still, W. C.; Tempczyk, A.; Hawley R. C.; Hendrickson, T. *J. Am. Chem.* Soc**. 1990**, *112***,** 6127.
(115) Eisenberg, D.; McLachlan, A. D. *Nature* **1986**, *319*, 199.
(116) Kozaki, T.; Morihashi, K.; Kikuchi, O. *J. Am. Chem. Soc*. **1989**, *111*, 1547.
(117) Saunders, M.; Houk, K. N.; Wu, Y. D.; Still, W. C.; Lipton, M.; Chang, G.; Guidal, W. C. *J. Am. Chem. Soc.* **1990**, *112,* 1419.
(118) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989,** *111***,** 4379.
(119) http://en.wikipedia.org/wiki/Autostereogram

(120) Mayo, K. H.; Ilyina, E.; Park, H. *Protein Science* **1996,** *5*, 1301.
(121) Thirumalai, D.; Klimov, D. K.; Dima, R. I. *Curr. Opin. Struct. Biol.* **2003,** *13*, 1.
(122) Richardson, J. S.; Richardson, D. C. *Proc. Natl. Acad. Sci. USA* **2002,** *99*, 2754.
(123) Zabrodsky, H.; Peleg, S.; Avnir, D. *IEEE Transactions on Pattern Analysis and Machine Intelligence* **1995,** *17*, 1154.
(124) Zabrodsky, H.; Avnir, D. *J. Am. Chem. Soc.* **1995,** *117*, 462.
(125) Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1993,** *115*, 11656.
(126) Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1993,** *115*, 8278.
(127) Buda, A. B.; Derheyde, T. A.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1992,** *31*, 989.
(128) Buda, A. B.; Mislow, K. *J. Am. Chem. Soc.* **1992,** *114*, 6006.
(129) Heyde, T.; Buda, A. B.; Mislow, K. *J. Math. Chem.* **1991,** *6*, 255.
(130) Aravinda, S.; Shamala, N.; Desiraju, S.; Balaram, P. *Chem. Commun.* **2002**, 2454.
(131) Bobde, V.; Sasidhar, Y. U.; Durani, S. *Int. J. Pept. Protein Res.* **1994,** *43*, 209.
(132) Clark, T. D.; Buehler, L. K.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1998,** *120*, 651.
(133) Convert, O.; Duplaa, H.; Lavielle, S.; Chassaing, G. *Neuropeptides* **1991,** *19*, 259.
(134) Ehrlich, A.; Heyne, H.-U.; Winter, R. D.; Beyermann, M.; Hanka Haber; Carpino, L. A.; Bienert, M. *J. Org. Chem.* **1996,** *61*, 8831.
(135) Formaggio, F.; Bettio, A.; Moretto, V.; Crisma, M.; Toniolo, C.; Broxterman, Q. B. *J. Pept. Sci.* **2003,** *9*, 461.
(136) Hong, S. Y.; Oh, J. E.; Lee, K. H. *Biochem. Pharmacol.* **1999,** *58*, 1775.
(137) Imperiali, B.; Fisher, S. L.; Moats, R. A.; Prins, T. J. *J. Am. Chem. Soc.* **1992,** *114*, 3182.
(138) Kiyota, T.; Yanagida, R.; Oka, M.; Miyoshi, M.; Lee, S.; Sugihara, G. *Bull. Chem. Soc. Jpn.* **2000,** *73*, 2363.
(139) Krause, E.; Beyermann, M.; Fabian, H.; Dathe, M.; Rothemund, S.; Bienert, M. *Int. J. Pept. Protein Res.* **1996,** *48*, 559.
(140) Krause, E.; Rothemund, S.; Beyermann, M.; Bienert, M. *Anal. Chim. Acta* **1997,** *352*, 365.
(141) Krause, E.; Bienert, M.; Schmieder, P.; Wenschuh, H. *J. Am. Chem. Soc.* **2000,** *122*, 4865.
(142) Lee, D. L.; Powers, J. P. S.; Pflegerl, K.; Vasil, M. L.; Hancock, R. E. W.; Hodges, R. S. *J. Pept. Res.* **2004,** *63*, 69.
(143) Maeda, M.; Melnyk, R. A.; Partridge, A. W.; Liu, L. P.; Deber, C. M. *Biopolymers* **2003,** *71*, 77.
(144) Mitchell, J. B. O.; Smith, J. *Proteins: Struct., Funct., Genet.* **2003,** *50*, 563.
(145) Rothemund, S.; Krause, E.; Beyermann, M.; Dathe, M.; Bienert, M.; Hodges, R. S.; Sykes, B. D.; Sonnichsen, F. D. *Peptide Research* **1996,** *9*, 79.
(146) Weisshoff, H.; Prasang, C.; Henklein, P.; Frommel, C.; Zschunke, A.; Mugge, C. *Eur. J. Biochem.* **1999,** *259*, 776.
(147) Wieprecht, T.; Dathe, M.; Schumann, M.; Krause, E.; Beyermann, M.; Bienert, M. *Biochemistry* **1996,** *35*, 10844.
(148) Gellman, S. H. *Acc. Chem. Res*. **1998**, *31*, 173.
(149) Giacovazzo, C. *Fundamentals of Crystallography;* Oxford University Press: Oxford, 2002.
(150) Englander, S. W.; Kanllenbach, N. R. Q. *Rev. Biophys*. **1984**, *16*, 521.
(151) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc*. **1996**, *118*, 13071.
(152) Stevens, E. S.; Sugawara, N.; Bonara, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7048.
(153) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512.

(154) Holzwarth, G. M.; Doty, P. *J. Am. Chem. Soc.* **1965**, *87*, 218.
(155) Engle, A. R.; Purdie, N.; Hyatt, J. A. *Carbohydr. Res.* **1994**, *265*, 181.
(156) Wiesler, W. T.; Berova, N.; Ojika, M.; Meyers, H. V.; Chang, M.; Zhou, P.; Lo, L.-C.; Niwa, M.; Takeda, R.; Nakanishi, K. *Helv. Chim. Acta* **1990**, *73*, 509.
(157) Perczel, A.; Kollat, E.; Hollosi, M.; Fasman, G. D. *Biopolymers* **1993**, *33*, 665.
(158) Melton, L. D.; Morris, E. R.; Rees, D. A.; Thom, D. *J. Chem. Soc., Perkin Trans. 2* **1979**, 10.
(159) Listowsky, I.; Avigad, G.; Englard, S. *J. Org. Chem.* **1970**, *35*, 1080.
(160) Comb, D. G.; Roseman, S. *J. Biol. Chem.* **1960**, *235*, 2529.
(161) Dewitt, C. W.; Zell, E. A. *J. Bacteriol.* **1961**, *82*, 849.
(162) Blacklow, R. S.; Warren, L. *J. Biol. Chem.* **1962**, *237*, 3520.
(163) McReynolds, K. D.; Gervay-Hague, J. *Tetrahedron: Asym.* **2000**, *11,* 337.
(164) Berova, N.; Nakanishi, K.; Woody, R. W. Circular Dichroism: Principles and Applications; 2nd Edition, Wiley-VCH, 2000.
(165) Rodger, A.; Norden, B. Circular dichroism and linear dichroism; Oxford University Press, 1997.
(166) Epand, R. M.; Scheraga, H. A. *Biopolymers* **1968**, *6*, 1551.
(167) Yaron, A.; Katchalski, E.; Berger, A.; Fasman, G. D.; Bover, H. A. *Biopolymers* **1971**, *10*, 1107.
(168) Conio, G.; Patrone, E. *Biopolymers* **1969**, *8*, 57.
(169) Conio, G.; Patrone, E.; Brighetti, S. *J. Biol. Chem.* **1970**, *245*, 3335.
(170) Satoh, M.; Fujii, Y.; Kato, F.; Komiyama, J. *Biopolymers* **1991**, *31*, 1.
(171) Bianchi, E.; Rampone, R.; Tealdi, A.; Ciferri, A. *J. Biol. Chem.* **1970**, *245*, 3341.
(172) Bello, J. *Biopolymers* **1993**, *33*, 491.
(173) Goodman, M.; Listowsky, L.; Masuda, Y.; Boardman, F. *Biopolymers* **1963**, *1*, 33.
(174) Goodman, M.; Rosen, I. G. *Biopolymers* **1964**, *2*, 537.
(175) Goodman, M.; Verdini, A. S.; Toniolo, C.; Phillips, W. D.; Bovey, F. A. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *64*, 444.
(176) Cammers, A.; Allen, T. J.; Oslick, S. L.; McClure, K. F.; Lee, J. H.; Kemp, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 3082.
(177) Zubay, G. L. *Biochemistry* 4th ed, Wm. C. Brown Publisher, 1998.
(178) Larrow, J. F., Jacobsen, E. N. *J. Org. Chem*. **1994**, *59*, 1939.
(179) Pikul, S.; Corey, E. J. *Organic Syntheses*, Vol 71, 1993.
(180) Skarzewski, J.; Gupta, A. *Tetrahedron: Asym.* **1997**, *8*, 1861.
(181) Nielsen, P. E. *Chem. Eur. J.* **1997**, *3*, 912.
(182) Xu, D., Prasad, K., Repic, O., Blacklock, T. J. *Tetrahedron Lett*. **1995**, *36*, 7357.
(183) Tye, H.; Eldred, C.; Wills, M. *Tetrahedron Lett.* **2002**, *43*, 155.
(184) Weygand, F.; Swodenk, W. *Chem. Ber*. **1957**, *90*, 639.
(185) Burgess, K. *Solid-Phase organic synthesis*; John Wiley & Sons: New York, 2000.
(186) Wang, S. S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.
(187) Jochims, J. C.; Seeliger, A. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 174.
(188) Smith, J.; Liras, J. L.; Schneider, S. E.; Anslyn, E. V. *J. Org. Chem.* **1996**, *61*, 8811.

Vita

Sihui Long was born on the 29th of June, 1975 in Hunan, China. He graduated from Ou Yangyu Middle School in 1993 as one of the top 5 students, then he was admitted to Wuhan University, arguably the most beautiful university and one of the prestigious universities in China. After 4 years of hard work there, he got his bachelor's degree in science and was admitted to the graduate school waived of admission exams as one of the top 20 graduates of the department. He spent another three years studying antiphytovirucides under the guidance of professor Fanqi Qu. In 2000, he graduated with a master's degree in science as one of the outstanding graduates of the department. In the same year, he left for University of Kentucky to pursue his PhD. In the past near 6 years, he has been working on peptidomimicry with chiral oligoureas under the wing of Professor Cammers as well as enjoying his life in a new country.

Publications resulting from this work

1. Sihui Long and Arthur Cammers* "Peptido Mimicry by C_2-Symmetric Oligoureas: Minimalist Cooperativity in the Global Conformation of Homochiral
and Alternating Heterochiral Chains" (manuscript)

Publications not included in this work

1. Sihui Long, Venkatraj Muthusamy, Peter G. Willis, Sean Parkin and
Arthur Cammers* "Benzimidazolecarboxamidines and Imidazolecarboxamidines: Directionality and the Solid State Hydrogen Bond Lattice at the Parametric Tipping Point between Dimer, N-mer and Tape" (manuscript)

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